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SYNTHESIS AND SCREENING OF NEW ANTIMALARIAL DRUGS

Final Report

M. M. Dhar

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1. Eight new compounds were evaluated for radical curative properties in the rhesus P. cynomolgi model. Eight additional compounds are currently under-going evaluation. 2. WR238605 was evaluated in the three day casual prophylactic test and found to be protective with a calculated CD_{50} of 0.125 mg/kg/day (molar primaquine index of 10.5). An extensive protocol was also completed to evaluate a single dose regimen of WR238605 in the causal prophylactic model. This drug was protective at 2.84 mg/kg when given 2 days prior to sporozoite challenge and protective at 5.68 mg/kg when given 3 days prior to sporozoite challenge. These data correlate well with the known pharmacokinetics of the drug. 3. The blood schizonticidal properties of chloroquine (active at 3 mg/kg/day x 7 days) were validated in trophozoite-induced infections and WR238605 was found to be curative at doses at low as 1.0 mg/kg/day x 7 days.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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SUMMARY OF THE ACHIEVEMENTS OF WRAIR- CDRI COLLABORATIVE PROJECT NO. DAMD17-82-G-9515

"SYNTHESIS AND SCREENING OF NEW ANTIMALARIAL DRUGS"

Achievements during the period Sept. 15,1982- September 14, 1987:

1. Protocols for the following antimalarial screening test systems have been established at CDRI.

(i) P.cynomolgi B/ A.stephensi /rhesus monkeys model has been successfully established and the parasite has undergone 38 serial cyclic passages to date.

(ii) Model for blood schizontocidal efficacy of known and new compounds in simian model has been established. Reference drug chloroquine has shown consistently curative action at 3 mg/kg (base) x 7 days. No escalation of chloroquine curative dose has been observed during the period of 37 cyclic passages.

(iii) Model for radical curative (anti-relapse) efficacy against sporozoite induced P.cynomolgi B established. Reference drug primaquine at 1 mg/kg (base) has been found to be consistently curative during last 4 years.

(iv) Model for causal prophylactic activity against sporozoite induced P.cynomolgi B infection hasbeen established. Initially a 9 day treatment schedule was used for prophylactic efficacy test. In view of the high priority of prophylactic test for WRAIR programme, a shorter 3 day treatment schedule (prophtlactic test) has been

standardized and a dose of 1.78 mg/kg (base) primaquine has been found to be consistently curative. Besides, prophylactic efficacy of primaquine in a single dose administration has been established and 5.34 mg/kg dose on day O has been found to be curative.

2. Screening of candidate drugs and selection of potential antimalarial compounds for radical curative and prophylactic activity developed by WRAIR and CDRI.

2.i) Radical curative (anti-relapse) efficacy of new compounds:

a) Fifteen new compounds have been identified to possess radical curative activity against P. cynomolgi B:

Order of antimalarial (anti-relapse) activity

i)	One compound active at 0.1 mg/kg (WR 242511)	Primaquine index 10.0
ii)	Seven compounds active at 0.316 mg/kg (WR 238605, WR249252, WR 254715, WR 254763, CDRI 85/276, CDRI 86/4, CDRI 86/6)	3.16
iii)	One compound active at 0.8 mg/kg (CDRI 83/382)	1.25
iv)	Five compounds active at 1.00mg/kg (CDRI 85/277, 85/278, 85/285, 85/403, 86/5)	1.00
v)	One compound active at 1.25mg/kg (CDRI 80/53)	0.8

2.ii) Preclinical toxicology of compound CDRI 80/53:

Methemoglobin toxicity studies in beagle dogs with compound CDRI 80/53 showed that this compound was relatively safe as compared to primaquine and its

toxicity was 3-4 times lower. Three month subacute toxicity studies in two hosts (rats and monkeys) have shown no adverse toxicity and compound is considered safe for Phase I clinicial trials after DCI clearance.

2.iii. Preclinical toxicology of compound WR 238605 :

Compound WR 238605, selected for anti-relapse activity under this screening programme has undergone subacute toxicity studies at WRAIR. The compound is considered safe and application is proposed to be submitted for IND approval.

2.iv. Causal prophylactic efficacy of new compounds

Five new compounds have been identified to possess causal prophylactic activity in 3 day treatment schedule (prophylactic test) against sporozoite induced infections of P.cynomolgi B.

Order of antimalarial (prophylactic) activity

Three day test

	Primaquine index
One compound active at 0.1mg/kg (WR 242511)	17.8
Three compounds active at 0.316mg/kg (WR 238605, WR 225448, WR 249420)	5.3
One compound active at 31.6 mg/kg(WR 197236)	

Single dose test

Three compounds (WR 242511, WR 230605 and WR 225448) have also shown prophylactic activity after single dose administration on day 0.

Compound WR 238605 screened at CDRI for prophylactic activity , showed promising activity and has been selected for IND approval by WRAIR.

PROGRESS REPORT OF THE JOINT COLLABORATIVE PROJECT NO. DAMD 17-82-G-9515 "Synthesis and Screening of New Antimalarial Drugs"

Collaboration Institutions:

1. Central Drug Research Institute, Lucknow (India) (CDRI).
2. Walter Reed Army Institute of Research, Washington, D.C. (U.S.A.) (WRAIR).

Period of Report: September 15, 1982 - September 14, 1987.

STANDARDIZATION OF SCREENING TEST SYSTEMS AT CENTRAL DRUG RESEARCH INSTITUTE

The protocol of "Program Plan for Institution of Research Collaboration" jointly developed in 1982 by WRAIR, Washington and CDRI, Lucknow was aimed at the establishment of reproducible test systems at CDRI, which should be comparable to the systems developed at WRAIR for evaluation and preclinical efficacy trials of potential blood schizontocides and radical curative and causal prophylactic antimalarial drugs being synthesized and developed by the US Army Antimalarial Drug Program and by CDRI. Comprehensive protocols have been developed for antimalarial efficacy tests. The test systems have been standardized using reference drugs and have been found to be reproducible.

PROTOCOLS DEVELOPED AT CENTRAL DRUG RESEARCH INSTITUTE, LUCKNOW IN COLLABORATION WITH WALTER REED ARMY INSTITUTE OF RESEARCH FOR DEVELOPMENT OF NEW ANTIMALARIAL DRUGS :

During the last five years, CDRI, Lucknow, has been working in close collaboration with WRAIR, Washington for standardization of experimental models for screening of new blood schizontocidal, radical curative (anti-relapse) and causal prophylactic agents and the pre-clinical efficacy trials of the compounds synthesized and developed by US Army antimalarial drug development programme and CDRI. This joint biomedical collaborative research programme has led to the establishment of reliable antimalarial screening models. The reproducibility of the following antimalarial screens at CDRI has been validated using standard drugs and it is encouraging to point out that our results with the standard drugs are in close agreement with the data obtained at AFRIMS, Bangkok and WRAIR Washington. The test systems are in operation and it is proposed to keep these antimalarial models for ongoing collaborative programme between CDRI and WRAIR.

A. Rhesus blood schizontocidal test - (P.cynomolgi) :

a) Maintenance of rhesus monkeys (M.mulatta).

Rhesus monkeys (4-5 kg) used for antimalarial screening programme are procured from approved Government Contractors, and kept under quarantine for four weeks. These monkeys are tuberculin tested before receiving them in the primate house and then after every 1 to 2 months. During quarantine period monkeys

are chest X-rayed and examined for absence of blood protozoans and three blood smears at weekly intervals are preserved for records. Tuberculin negative monkeys free from any blood parasites are transferred to experimental wing and kept in mesquito free rooms. They are supplied standard pellet diet, seasonal fruits, vegetables and water ad libitum. The monkeys are kept under 12 hr photoperiodicity.

b) Parasite : Plasmodium cynomolgi B procured in 1979 from Dr. W.E. Collins, CDC, Atlanta, has been maintained in CDRI by successive blood induced passages as well as by cryopreservation. During the current ~~xx~~ WRAIR-CDRI project, the parasite P. cynomolgi has been transmitted through Anopheles stephensi for 37 consecutive passages and the parasite taken from patent infection has been used from time to time for standardization of blood schizontocidal test using chloroquine diphosphate as the reference drug.

For blood induced infections, the rhesus monkeys are infected with $1x10^5$ parasitized RBC in 1 ml. of acid- citrate dextrose (ACD) intravenously and blood smears are examined daily for patency. The parasitaemia is recorded in terms of number of parasites /mm^3 from thick or thin blood smears. At the patency, the parasitaemia is recorded in thick smears on the basis of number of parasites per 50 oil immersion fields. The parasite number multiplied by 20 gives parasitaemia/mm^3. When number of parasites /50 thick fields is more than 50, further recording is made from thin films by determining the number of parasites/100 WBC, and parasitaemia/ mm^3 is calculated after recording number of WBC/mm^3 using haemocytometer. Finally when number of parasites/

e) Determination of chloroquine curative dose :

(1.0 mg chloroquine base = 1.62 mg chloroquine diphosphate)

In order to determine 100% curative dose of chloroquine against blood induced P.cynomolgi B in rhesus monkey, the initial infective inoculum was taken from monkey infected by sporozoites. For conducting the blood schizontocidal test, five groups of monkeys each were given $1x10^5$ parasitized RBC by i/v route and when the parasitaemia had reached 0.1 to 0.5% level (5,000 - 20,000/mm^3), each group (5 monkeys) was administered chloroquine dosages of 1.0, 3.0, 5.0, 7.0 and 10.0 mg/kg (base) for 7 days by oral route. Both thick and thin smears were examined daily to monitor the course of parasitaemia. Our results show that all the 5 monkeys at 1 mg/kg dose showed recrudescence, while those at 3.0, 5.0, 7.0 and 10.0 mg/ml were cured radically and showed no recrudescence till day 30. The 5 monkeys showing recrudescence of parasitaemia at 1.0 mg/kg were retreated with the next higher dose i.e. 3.0 mg/kg x 7 days. This dose was again found to be curative and no recrudescence was observed till 30 days.

Revalidation of curative dose of chloroquine: Three batches of 5 monkeys were given blood induced infection from a sporozoite infected monkey. When the parasitaemia had reached 0.1 to 0.5% level, they were administered chloroquine at 3.0, 5.0 and 7.0 mg/kg (base) x 7 days by oral route, and all the monkeys were followed for 30 days. All the three doses were again found to be curative.

Both initial curative tests and revalidation tests thus show that 3.0 mg/kg x 7 doses of chloroquine (base) have curative action on blood induced P.cynomolgi B. Although 3.0 mg/kg chloroquine has been found to be consistantly curative, we prefer to use

5 mg/kg chloroquine as the curative dose for radical curative tests. This dose we have used in radical curative tests and we have found it satisfactory.

B. RHESUS RADICAL CURATIVE (ANTI-RELAPSE) TEST :

Simian malaria parasite P.cynomolgi B, which closely resembles to human malaria P.vivax in its biological characteristics and relapse patterns, has been used for anti-relapse efficacy test using 7 day treatment radical curative test.

Primaquine has been used as the reference anti-relapse drug and chloroquine has been invariably used as the companion blood schizontocide. Both the drugs were administered orally. Although chloroquine is known to have no efficacy against tissue stages of P.cynomolgi which causes relapse of blood parasitaemia, we have to use chloroquine as a companion blood schizontocide in curative doses to effectively eliminate all blood parasitaemia from patent monkeys. From the day of sporozoite inoculation upto day 8, the primary tissue stages of P.cynomolgi B develop in the hepatocytes and after completion of phase of primary exo-erythrocytic cycle, the parasite invade blood and infect red blood cells. Generally, the monkeys become patent (i.e. slide positive blood smears) on day 8-12 depending upon the sporozoite inoculum. Once the monkey becomes patent, as shown by blood smear examination, there is 100% evidence of establishment of sporozoite induced malaria infection in the rhesus monkey. In order to study the effect of primaquine and related compounds on secondary tissue stages (Hypnozoites; which cause relapse), we have to administer a totally curative dose of chloroquine to eradicate blood infection.

A total curative dose of chloroquine would ensure elimination of all asexual erythrocytic stages and if the chloroquine dosing is inadequate, it would lead to recrudescence of parasitaemia, thus interfering with the interpretation of radical curative efficacy of test compound. Any patent infection after curative chloroquine treatment would be interpreted as relapse due to failure of the antirelapse test compound.

a) Insectary : In order to develop technology for large-scale sporozoite production for rhesus monkey inoculation, a large-scale rearing of Anopheles stephensi (NICD Strain) for transmission studies had been set up. The insectary maintains routine egg-laying capacity of 2000- 4000, which ensures the availability of all the four larval instars at all times. Rhesus monkey has been found to be ideal for giving blood meal to mosquitoes for egg laying. The larval stages are fed on powdered yeast ~~hamster chow (supplied by AFRIMS)~~ and maintained at 25 ± 1°C. The pupation starts after 8-10 days and adults emerge 36 to 48 hr later. The adults are maintained at 26 ± 1°C with relative humidity 75 to 80%, and fed on 5% multivitamin solution.

b) Infection of mosquitoes : In order to infect the Anopheles stephensi mosquitoes, the daily course of parasitaemia /gametocytaemia in a control (untreated) monkey is recorded. Primary peak parasitaemia is attained 7-10 days after patency and secondary peak is observed 5-8 day later. Mosquito infectivity studies at CDRI during the last 5 years have shown that ideal infection rate is obtained when mosquitoes are fed on monkeys at the declining phase of secondary peak.

Two to three days old female mosquitoes are fed on infected rhesus monkeys showing optimum gametocyte number/ratio. The monkey is anaesthatized with sodium intraval (20 mg/kg i/v) and mosquitoes are allowed to have blood meal for 20-30 minutes.

On day 7 after blood meal, 5 mosquitoes from each of the infected batches are dissected for determining the number of oocysts on the gut. The mean number and the size of the oocysts is recorded, which generally ranges between 30-50 in number and 40- 50μ in size.

c) Estimation of sporozoite number in infected mosquitoes:

On day 13 after blood meal, (or one day prior to inoculation of monkeys), the sporozoite number is estimated in the mosquitoes from the batch which has earlier been found to show high oocysts number (on day 7). Ten infected mosquitoes were used for preparing sporozoite inoculum using rhesus serum saline as diluent.

d) Sporozoite infection : On the day of inoculation, the required number of mosquitoes (determined from estimate count on day 13) are homogenized in 1:1 serum-saline mixture, and centrifuged at 2000 rpm for 1 min. to settle the major mosquito debries. The sediment is once again suspended in serum-saline mixture, recentrifuged and supernatant added to the first supernatant. The total volume is made up with serum-saline mixture so as to obtain $1x10^5$ - $1x10^6$ sporozoites in one ml.

Each monkey is inoculated intravenously, one ml of inoculum and blood smear are examined daily from day 7 onwards.

e) Determination of Primaquine curative dose :

(1 mg primaquine base = 1.76 mg primaquine -diphosphate)

For the determination of the radical curative dose of primaquine 2 monkeys each were treated orally at 0.180, 0.316, 0.563, 0.739, 1.0, 1.3, 1.795 and 5.680 mg (base)/kg dose levels. The treatment was initiated when blood parasitaemia reached 5000/mm^3 and administered once daily for seven days. The blood smears were examined for 90 days after end of treatment for appearance of relapse infection. The results showed that monkeys treated at 0.180 mg/kg and 0.316 mg/kg relapsed while monkeys treated at higher doses were cured. The relapsing monkeys were re-treated at 1.0 mg (base)/kg dose x 7 days and these monkeys were cured.

For the revalidation of radical curative dose, the treatment was given orally at 1.0 mg/kg dose to 8 monkeys and 1.3 mg/kg to 5 monkeys. All the 13 treated monkeys were cured of infection. The dose of 1.0 mg /kg (base) is being used as the standard radical curative dose in our study. This dose of primaquine is combined with 5 mg/kg ((base) chloroquine as the curative blood schizontocidal drug. Although initial reports from Walter Reed indicated escalation of radical curative primaquine dose and chloroquine curative dose over the years at AFRIMS, the dose standardization carried out at CDRI has been much more consistent in successive cyclic passages during the last 4 years and no escalation of primaquine/chloroquine curative doses has been observed at CDRI.

C. Rhesus Prophylactic Test :

The methodology for initiating sporozoite induced infections with P.cynomolgi B in rhesus monkey has been described above under radical curative test, ~~a three day treatment~~ A three day treatment and the same has been applied in the prophylactic test. model has been standardized for evaluation of potential causal prophylactic compounds. In this model, the drug treatment is administered on days-1, 0 and +1 and sporozoite infection is inoculated on day 0. The blood smears are examined from day 7 onwards till day 70 for observing the patency in experimental animals. This model has advantage over conventional 9 day treatment model developed by ~~Sch~~ Schmidt, since the treatment schedule is for shorter duration.

a) Sporozoite infection : The method for obtaining sporozoites from A.stephensi is described under radical curative test.

b) Drug administration : The test drug is administered for three doses (on day -1, day 0, day +1 of sporozoite inoculation) orally in 10 ml. volume. The drug/test compound is suspended in 0.3% methyl cellulose solution.

c) Determination of primaquine prophylactic dose :

For determining the prophylactic dose of primaquine, experimental monkeys were treated at 0.316 mg/kg, 1.00 mg/kg, 1.78 mg/kg, 3.16 mg/kg and 10.0 mg/kg x 3 day, dose levels. Our results showed that monkeys treated at 0.316 mg/kg, and 1.00 mg/kg became patent while higher doses of 1.78 mg/kg and above were curative. The curative dose of 1.78 mg/kg has been revalidated several times during the 37 successive cyclic passages of P. cynomolgi B and this dose is being used as the standard reference dose in our study. This test system was not operational at

WRAIR/AFRIMS and has been standardized at CDRI

The following additional antimalarial screens are proposed to be standardized at CDRI. The following protocols will be used.

D. Rhesus Gametocytocidal/ Sporontocidal Test :

No standardized technique for determining gametocytocidal activity/sporontocidal action of new compound against vivax type of simian malaria namely P.cynomolgi B has been developed so far. Primaquine is the only standard gametocytocidal drug available and there is urgent need to screen the primaquine analogues which have shown high anti-relapse activities and establish their gametocytocidal/sporontocidal activity. Under the continuing programme of CDRI-WRAIR collaborative project, it is proposed to initiate studies on the development of this test using P.cynomolgi - A.stephensi model. The capability of producing infectivity in the mosquitoes, recording of gametocytaemia, oocyst count, etc. are routinely carried out under the existing project. The experience and expertise available at WRAIR and CDRI will be used to develop this new test system for developing compounds showing gametocytocidal activity which will have a role in interrupting of transmission cycle.

Since a number of new compounds have been identified which are less toxic than primaquine this new screening system has a great promise to develop safe gametocytocidal drugs. The test system for gametocytocidal/sporontocidal activity reported by Rieckmann et al.,1969; (Milit.Med. 134: 802-819) will be further validated and improved to make it more specific. Primaquine will be used as the reference drug for standardization of the model.

E. In-vitro screening of anti-malarials :

It is proposed to develop the research capability at CDRI for long term in vitro cultivation of P.falciparum and further establish the technology for in vitro screening of anti-malarial drugs. The semi-automated screening facility for large-scale anti-malarial screening will be an asset for our programme of development of new anti-malarials. The quantitation of in vitro activity will be done by incorporation of H^3-Hypoxanthine in cultures incubated with drug dilutions and the end-points will be recorded according to the technique of Desjardins et al., (1979), Antimicrobiol agents and chemotherapy 16, 710-718), Milhous et al.,(1985), Antimicrobiol agents and chemotherapy, 27, 525-530). The test system will be similar to the one in operation at WRAIR,Washington. High level of quantitation can be obtained by this anti-malarial screen and very little quantity of compound is needed for in vitro assay.

F. PROTOCOL FOR CYCLIC PASSAGE OF P.CYNOMOLGI B

P.cynomolgi B in monkey attains primary peak parasitaemia of 4,00,000 - 8,00,000/mm^3 in 7-8 days after patency. The parasite number then declines without any treatment and the secondary peak parasitaemia of 30,000-60,000/mm^3 is observed 4-5 days later. Initial studies at AFRIMS have shown that maximum infectivity of mosquitoes is observed when they are fed on infected monkeys during the secondary peak parasitaemia. Moreover, a ratio of 3:1 for female to male gametocytes has been found to be ideal for obtaining maximum infectivity. In order to ensure high infectivity of mosquitoes, the above practice is followed.

d) Infection of mosquitoes

Two or three days old female mosquitoes (Anopheles stephensi) are fed on infected rhesus monkeys showing optimum gametocyte number/ratio. The monkey is anaesthetized with sodium interval (20 mg/kg i/v) and mosquitoes are allowed to have ~~blood~~ blood meal for 20-30 minutes. Three batches of mosquitoes are fed on each monkey on three consecutive days. The fed mosquitoes are kept in insectary whereas the males and unfed females from each cage are discarded.

On day 7 after blood meal, 5 mosquitoes from each of the infected batch are dissected for determining the number of oocyst on the gut. The mean number and the size of the oocysts is recorded, which generally ranges between 20-50.

b) Estimation of sporozoite number of infected mosquitoes

On day 13 after blood meal (or one day prior to inoculation of monkeys), the sporozoite number is estimated in the mosquitoes from the batch which has earlier been found to show high oocyst number on day 7. The infected mosquitoes from the sample batch are anaesthetized and legs, wings, head and abdomen are removed. The thoraces are grinded with a mixture of 0.5 ml saline and 0.5 ml rhesus normal serum (total 1ml). With the help of a graduated capillary (or an *appendorf pipette*), 5 µl of the sporozoite suspension is applied and spread within the etched circle of a FA slide. The slide is allowed to air dry, fixed in methanol (5 minutes) and stained with Giemsa stain for 40 minutes. The number of sporozoites/100 oil immersion fields is counted in two slides and the mean value multiplied by the magnification factor of the microscope gives the sporozoite number per ml of solution or the sporozoite number/10 infected mosquitoes. (The magnification factor for our microscope as determined by using a slide/stage micrometer is 10974. From this estimation, the number of mosquitoes required to obtain 1 million sporozoites/monkey can be determined.

C) Harvesting of sporozoites for inoculation

On day 14, sporozoites are harvested from the infected mosquitoes for inoculation into rhesus monkeys. Required number of mosquitoes (determined on the basis of estimation made on day 13) are anaesthetized by keeping them for 2-3 minutes in a referigerator and their legs and wings are removed. For all further processes the mosquitoes are kept over ice to

maintain the infectivity of sporozoites. The head and abdomen of the mosquitoes are removed with a scalpel and thoraces are put in a chilled pestle mortar for grinding. The grinding is carried out in cold using 1:1 mixture of normal saline and normal rhesus serum. After grinding, the suspension is centrifuged at 1000 rpm for 15 seconds at 4°C. The sediment is discarded and the supernatant is diluted with serum/saline mixture to get the required inoculum. (Nearly 50% of the sporozoites are lost with the debries after centrifugation). The whole process after anaesthetization of mosquitoes to the inoculation of monkeys should be completed within 45-60 minutes. Each monkey is inoculated via i/v route with 1 ml of the inoculum, and the exact number of sporozoites inoculated per monkey is determined from the sample inoculum.

d) Serial cyclic passage of sporozoite induced infection in rhesus monkey.

The recording of parasitaemia in first to fifth passage was made using thin blood films for recording patency. After 5th passage the parasites were kept frozen for nearly 4 months. The gametocytes of the monkey infected with frozen blood were used for infection and for initiation of the 6th passage. In subsequent passages, the patency was recorded from thick smears. Improved method of sporozoite count was also introduced at this stage following the training of Dr. S.K. Puri at AFRIMS. To date the strain of P.cynomolgi B has been cyclically transmitted through A.stephensi for 38 passages.

CORI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

BLOOD INDUCED TEST

WR: 1544 (CHLOROQUINE) (Determination of curative dose)

BN: AA 20613

DATE REC'D: October, 1982

QUANTITY: 25 gm

VEHICLE: Aqueous

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg)× 7 days	MONKEY #	RESULT
1.0 mg/kg	1741	Recrudescence on day 12
1.0 mg/kg	1742	Recrudescence on day 11
1.0 mg/kg	1745	Recrudescence on day 11
1.0 mg/kg	[illegible]	Recrudescence on day 10
1.0 mg/kg	1749	Recrudescence on day 10
3.0 mg/kg	1741*	No Recrudescence till day 30
3.0 mg/kg	1742*	No recrudescence till day 30
3.0 mg/kg	1745*	No recrudescence till day 30
3.0 mg/kg	1748*	No recrudescence till day 30
3.0 mg/kg	1749*	No recrudescence till day 30

*monkeys retreated with chloroquine after recrudescence at the lower dose level.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** ~~SPOROZOITE INDUCED TEST~~ ***

BLOOD INDUCED TEST

WR: 1544 (CHLOROQUINE) (Determination of curative dose)

BN: AR 20613

DATE REC'D: October, 1982

QUANTITY: 25 gm

VEHICLE: Aqueous

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) x 7 days	MONKEY #	RESULT
3.0 mg/kg	1750	No recrudescence till day 50
3.0 mg/kg	1751	No recrudescence till day 50
3.0 mg/kg	1752	No recrudescence till day 50
3.0 mg/kg	1753	No recrudescence till day 50
3.0 mg/kg	1754	No recrudescence till day 50
5.0 mg/kg	1735	No recrudescence till day 50
5.0 mg/kg	1736	No recrudescence till day 50
5.0 mg/kg	1737	No recrudescence till day 50
5.0 mg/kg	1739	No recrudescence till day 50
5.0 mg/kg	[illegible]	No recrudescence till day 50

CDRI PRIMATE ANTIMALARIAL STUDY (5)
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***
BLOOD [illegible] TEST

WR: 1544 (CHLOROQUINE) (Determination of curative dose

BN: AR 20613

DATE REC'D: October, 1982

QUANTITY: 25 gm

VEHICLE: Aqueous

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg)× 7 days	MONKEY #	RESULT
7.0 mg/kg	1738	No recrudescence till day 50
7.0 mg/kg	1743	No recrudescence till day 50
7.0 mg/kg	1744	No recrudescence till day 50
7.0 mg/kg	1747	No recrudescence till day 50
7.0 mg/kg	1748	No recrudescence till day 50
10.0 mg/kg	1727	No recrudescence till day 50
10.0 mg/kg	1728	No recrudescence till day 50
10.0 mg/kg	1729	No recrudescence till day 50
10.0 mg/kg	1730	No recrudescence till day 50
10.0 mg/kg	1731	No recrudescence till day 50

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** ~~SPOROZOITE INDUCED~~ TEST ***

BLOOD INLUCED TEST

.1544 (CHLOROQUINE) (Revalidation of curative dose)

SN: AR 20613

DATE REC'D: October, 1982

QUANTITY: 25 gm

VEHICLE: Aqueous

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg)x 7 days	MONKEY #	RESULT
3.0 mg/kg	1722	No recrudescence till day 28
3.0 mg/kg	1723	No recrudescence till day 28
3.0 mg/kg	1779	No recrudescence till day 28
3.0 mg/kg	1781	No recrudescence till day 28
3.0 mg/kg	1791	No recrudescence till day 28
5.0 mg/kg	1784	No recrudescence till day 28
5.0 mg/kg	1785	No recrudescence till day 28
5.0 mg/kg	1786	No recrudescence till day 28
5.0 mg/kg	1787	No recrudescence till day 28
5.0 mg/kg	1790	No recrudescence till day 28
7.0 mg/kg	1773	No recrudescence till day 28
7.0 mg/kg	1780	No recrudescence till day 28
7.0 mg/kg	1783	No recrudescence till day 28
7.0 mg/kg	1788	No recrudescence till day 28
7.0 mg/kg	1792	No recrudescence till day 2.

Date: April 15, 1987

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CHLOROQUINE

(Revalidation studies during sporozoite passage No. XXXV).

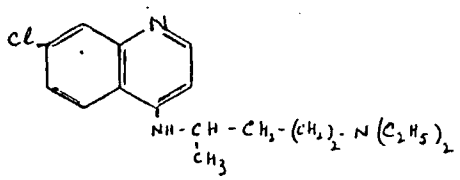
BN: AU 29291

DATE REC'D: Oct.'86

QUANTITY: 200 gm.

VEHICLE: Distilled Water

ROUTE: Oral



BLOOD SCHIZONTOCIDAL ACTIVITY (7 day treatment)

DOSE (mg/kg)	MONKEY #	RESULT
5.0	4410	Cured
5.0	4413	Cured
5.0	4416	Cured
3.0	4412	Cured
3.0	4414	Cured
3.0	4415	Cured
1.0	4407	Recrudescence on day 25
1.0	4408	Recrudescence on day 17
1.0	4409	Recrudescence on day 11

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 2975 PRIMAQUINE — Determination of curative dose

BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

	DOSE (mg/kg) x 7 day (base)	MONKEY #	RESULT
Expt. I	0.180	1673	Relapse on day 10
	0.180	1674	Relapse on day 10
	0.568	1677	No relapse till day 120
	0.568	1679	No relapse till day 120
	0.739	1680	No relapse till day 120
	0.739	1682	No relapse till day 120
	1.795	1676	No relapse till day 120
	1.795	1678	No relapse till day 120
	5.680	1675	No relapse till day 120
	5.680	1681	No relapse till day 120
	1.00*	1673	No relapse till day 130
	1.00*	1674	No relapse till day 130

*monkey retreated after relapse at the lower dose (0.130 mg/kg) leve

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 2975 PRIMAQUINE — Determination of curative dose

BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

	DOSE (mg/kg) × 7 day(base)	MONKEY #	RESULT
Exp.II	0.316	1733	Relapse on day 18
	0.316	1734	Relapse on day 28
	1.00	1724	No relapse till day 125
	1.00	1726	No relapse till day 125
	1.30	1720	No relapse till day 125
	1.30	1732	No relapse till day 125
	1.00*	1733	No relapse till day 100
	1.00*	1734	No relapse till day 100

*monkey retreated after relapse at the lower dose (0.316 mg/kg) leve

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 2975 Primaquine

BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY #	RESULT
1.0	1675	No relapse till day 100
1.0	1679	No relapse till day 100
1.0	1681	No relapse till day 100
1.0	1682	No relapse till day 100
1.0	1903	No relapse till day 100
1.0	1904	No relapse till day 100
1.0	1906	No relapse till day 100
1.0	1907	No relapse till day 100
1.3	1680	No relapse till day 100
1.3	1899	No relapse till day 100
1.3	1900	No relapse till day 100
1.3	1902	No relapse till day 100
1.3	1908	No relapse till day 100

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 2975 Primaquine

BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Normal seline

ROUTE: Intra-venous

RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY #	RESULT
1.0	2102	No relapse till day 100
1.0	2109	No relapse till day 100
1.0	2112	No relapse till day 100
2.0	2108	No relapse till day 100
2.0	2103	No relapse till day 100

Annexure - 1

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: PRIMAQUINE

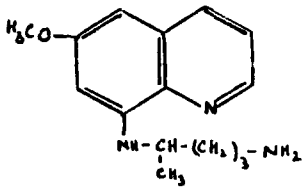
BN: SIGMA PRODUCT

DATE REC'D: OCT.' 1982

QUANTITY: 50 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg)	MONKEY #	RESULT
1.00	2704	No relapse till Day 100
1.00	2705	No relapse till Day 100
0.56	2753	No relapse till day 100
0.56	2754	No relapse till day 100
0.56	2755	No relapse till day 100
0.56	2757	No relapse till day 100

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: PRIMAQUINE

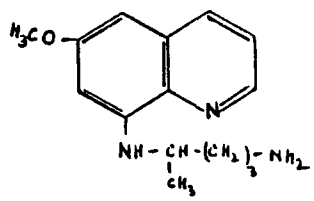
BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg)	MONKEY #	RESULT
1.00	3310	No relapse till Day 100
1.00	3313	No relapse till Day 100
1.00	3288	No relapse till day 100
1.00	3291	No relapse till day 100
0.56	3308	Patent on day 13
0.56	3311	Patent on day 26
0.56	3312	No relapse till day 100
0.56	3314	No relapse till day 100
0.56	3315	No relapse till day 100

*** SPOROZOITE INDUCED TEST ***

WR: 2075 Primaquine

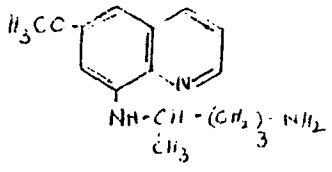
BN:

DATE REC'D:

QUANTITY:

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base*	MONKEY #	RESULT
1.00	2959	Cured
1.00	2960	Cured
1.00	3336	Cured
1.00	3220	Cured
1.00	3559	Cured
1.00	3562	Cured
1.00	3827	Cured
1.00	3831	Cured
1.00	3828	Cured
1.00	3921	Under test -ve till day 44

*Chloroquine @ 5 mg/kg. base x 7 days was used as a combination drug.

CDRI [illegible] PRIMAQUINE STUDY
PLASMODIUM [illegible] - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

DR: 2975 PRIMAQUINE

BN: SIGMA PRODUCT

DATE REC'D: OCT. 1982

QUANTITY: 50 gm

VEHICLE: Normal saline

ROUTE: Intra-venous

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
Expt.I (Sporozoite inoculation on 27.9.1983)		
0.5	2103	Patent on day 19
0.5	2112	Patent on day 24
1.0	2109	Patent on day 28
1.0	2110	No patency till day 60
Control	2102	Patent on day 9
Control	2108	Patent on day 9
Expt.II (Sporozoite inoculation on 8.11.1983)		
2.00	2339	No patency till day 70
2.00	2340	No patency till day 70
Control	2227	Patent on day 8
Expt.III (Sporozoite inoculation on 12.11.1983)		
2.00	2231	No patency till day 60
2.00	2232	No patency till day 60
Control	2229	Patent on day 9

Contd.....

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM [illegible] - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: PRIMAQUINE

EN:

DATE RECD:

QUANTITY:

VEHICLE:

ROUTE:

PROPHYLACTIC TEST

DOSE (mg/kg)	MONKEY #	RESULT
Contd.....		
Expt.IV (Sporozoite inoculation on 16.11.1983)		
1.00	2281	No patency till day 60
1.00	2282	No patency till day 60
1.00	2283	No patency till day 60
1.00	2284	No patency till day 60
Control	2230	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WP: 2975 PRIMAQUINE

BN: SIGMA PRODUCT

DATE REC'D: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
Expt.I (Sporozoite inoculation on 2.2.1983)		
0.316	1727	Patent on day 15
0.316	1728	Patent on day 13
1.0	1729	No patency till day 60
1.0	1730	No patency till day 60
1.30	1738	No patency till day 60
1.30	1741	No patency till day 60
3.16	1739	No patency till day 60
3.16	1740	No patency till day 60
10.00	1735	No patency till day 60
10.00	1736	No patency till day 60
Control	1719	Patent on day 10
	1731	Patent on day 11

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM KNOWLESI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

1/X: 2975 PRIMAQUINE

EN: SIGMA PRODUCT

DATE RECD: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)(base	MONKEY #	RESULT
Expt.II (Sporozoite inoculation on 9.4.1983)		
0.316	1675	Patent on day 17
0.316	1679	Patent on day 11
0.316	1681	Patent on day 13
0.316	1682	Patent on day 18
0.62	1680	Patent on day 18
0.62	1899	Patent on day 17
0.62	1900	Patent on day 16
0.62	1902	Patent on day 17
0.62	1908	Patent on day 17
1.00	1901	No patency till day 60
1.00	1903	Patent on day 22
1.00	1904	Patent on day 21
1.00	1906	Patent on day 21
1.00	1907	Patent on day 20
Control	1811	Patent on day 11
	1814	Patent on day 11

CDRI PRIMARY ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 2975 (PRIMAQUINE)

SA: SIGMA PRODUCT

DATE RECD: Oct. 1982

QUANTITY: 50 gm

VEHICLE: Methyl cellulose

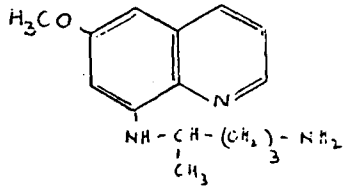
ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
Expt.III (Sporozoite inoculation on 26.12.1983)		
1.00	2354	No patency till day 60
1.00	2355	No patency till day 60
1.78	2358	No patency till day 60
1.78	2359	No patency till day 60
3.16	2349	No patency till day 60
3.16	2351	No patency till day 60
10.00	2352	No patency till day 60
10.00	2353	No patency till day 60
Control	2356	Patent on day 9
	2357	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: **2975 PRIMAQUINE**



VS: SIGM. PRODUCT

DATE REC'D: 0[illegible].'84

QUANTITY: 5[illegible] gm.

VEHICLE: [illegible]thyl cellulose

ROUTE: [illegible]l

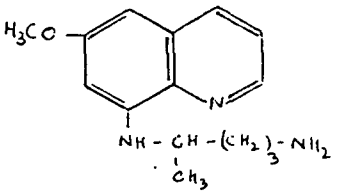
PROPHYLACTIC TEST

DOSE (mg/kg) (Base)	MONKEY NO.	TEST
EXPT.IV. : Sporozoite inoculation on 21.3.1984		
1.00	2232	No patency till day 70
1.00	2233	Patent on day 33
3.16	2221	No patency till day 7[illegible]
3.16	2226	No patency till day 7[illegible]
Control	2231	Patent onday 8.
	2234	Patent on day [illegible]
EXPT.V. : Sporozoite inoculation on 27.3.84		
1.00	2508	No patency till day 7[illegible]
1.00	2509	Patent on day 1[illegible]
1.00	2510	No patency till day 7[illegible]
1.00	2511	No patency till day 7
1.00	2516	Patent on day 1[illegible]
1.7[illegible]	2[illegible]	[illegible]
1.7[illegible]	[illegible]	[illegible]
1.7[illegible]	[illegible]	[illegible]

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 2975 PRIMAQUINE (Contd.)



'N: SIGMA PRODUCT

ATE REC'D: OCT. 1982

UANTITY: 31 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
1.78	2518	No patency till day 70.
1.78	2519	No patency till day 70.
3.16	2514	No patency till day 70
3.16	2520	No patency till day 70
3.16	2521	No patency till day 70
3.16	2522	No patency till day 70
3.16	2430	No patency till day 70
Vehicle:Control	2334	Patent on day 8
	2335	Patent on day 8.
EXPT.VI. Sporozoite inoculation on 7-9-84		
1.78	2798	No patency till day 70
1.78	2799	No patency till day 70
Vehicle Control	2775	Patent on day 9
EXPT.VII: Sporozoite inoculation on 11.10.84		
1.78	31 1	No patency till day 70
1.78	3 13	No patency till day 70
Control	3 12	Patent on day 11.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: PRIMAQUINE

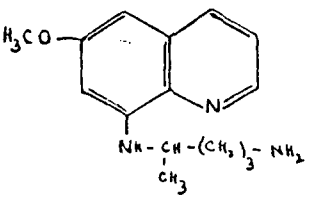
UN: SIGMA PRODUCT

DATE REC'D: OCT.,'82

QUANTITY: 50 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day Test)

DOSE (mg/kg)	MONKEY NO.	RESULT
I. Sporozoite Inoculation on 13-5-85 (Sp.passage No.XXI)		
1.78	3220	No patency till day 70
II. Sporozoite inoculation on 19-6-85 (Sp.passage No. XXII)		
1.78	3334	No patency till day 70
III. Sporozoite inoculation on 26-7-85 (Sp.passage No. XXIII)		
1.78	3363	Under test (no patency till day 50)
1.78	3364	Under test (no patency till day 50).

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 2975 (Primaquine)

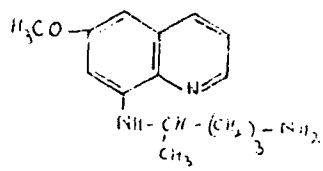
DN:

DATE REC'D:

QUANTITY:

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day treatment)

DOSE (mg/kg)	MONKEY NO.	RESULT
I. Sporozoite passage No. XXIII		
1.78	3363	Cured
1.78	3364	Cured
II Sporozoite passage No. XXIV		
1.78	3475	Cured
1.78	3476	Cured
III. Sporozoite passage No. XXV		
1.78	3582	Cured
IV Sporozoite passage No. XXVIII		
1.78	3683	Cured
1.78	3755	Cured
V. Sporozoite passage No. XXIX		
1.78	3813	Cured
VI. Sporozoite passage No. XXX.		
1.78	3913	Cured
1.78	3914	Cured

Serial cyclic passages of sporozoite induced *P.cynomolgi* B in rhesus monkeys.

Sporozoite passage no.	Date of inoculation	Monkey No.	Sporozoite inoculation (i.v.)	Day of Patency
I	6.11.82	1617	1×10^6	Day 10
II	17.12.82	1726	1×10^6	Day 12
III	2. 2.83	1719	1×10^6	Day 10
	2. 2.83	1731	1×10^6	Day 11
IV	7. 3.83	1832	1×10^6	Day 10
V	9.4 .83	1821	1×10^6	Day 11
		1844	1×10^6	Day 11
VI	27. 9.83	2102	0.68×10^6	9
VI	27. 9.83	2103	0.68×10^6	9
VI	7.10.83	2226	0.60×10^6	9
VII	8.11.83	2227	0.70×10^6	8
VII	12.11.83	2229	0.91×10^6	9
VII	16.11.83	2238	0.74×10^6	9
VII	22.11.83	2192	1.0×10^5	9
VIII	17.12.83	2197	0.54×10^6	9
VIII	17.12.83	2336	0.54×10^6	9
VIII	26.12.83	2351	0.66×10^6	9
	26.12.83	2357	0.66×10^6	9
VIII	6. 1.84	2371	0.85×10^6	8
IX	22.1 .84	2327	0.93×10^6	9
		2378	0.93×10^6	9

Table Conta.....

Table Contd.....

Sporozoite passage no.	Date of inoculation	Monkey No.	Sporozoite inoculation (i.v.)	Day of Patency
IX	24.1.84	2231	0.81×10^6	9
		2232	0.81×10^6	9
IX	24.1.84	2396	0.67×10^6	9
X	20.2.84	2242	0.64×10^6	9

CDRI PRIMATE ANTI-MALARIAL STUDY

Serial passages of sporozoite induced P.cynomolgi B infection

SPOROZOITE PASSAGE NO.	MONKEY NUMBER	DATE OF INOCULATION	SPOROZOITE INOCULUM (I.V.)	DAY OF PATENCY
X.	2282	20.2.84	0.64×10^6	9
	2325	5.3.84	0.75×10^6	9
	2337	5.3.84	0.75×10^6	9
XI.	2354	27.3.84	1.1×10^6	8
	2355	27.3.84	1.1×10^6	8
	2542	21.4.84	0.65×10^6	9
XII.	2569	23.5.84	0.7×10^6	9
XIII.	2642	19.6.84	0.82×10^6	8
XIV.	2644	30.7.84	0.82×10^6	8
XV	2775	7.9.84	0.66×10^6	9
	2803	7.9.84	0.68×10^6	9
XVI	2811	17.10.84	0.66×10^6	9
	2812	19.10.84	$0,58 \times 10^6$	10
	2917	22.10.84	0.72×10^6	9
XVII	2963	4.12.84	0.66×10^6	9
	2964	4.12.84	0.66×10^6	9

CDRI PRIMATE ANTI-MALARIAL STUDY

TABLE 1. Serial passages of sporozoite induced P.cynomolgi B infection

Sporozoite Passage No.	Monkey number	Date of inoculation	Sporozoite inoculum (i.v.)	Day of patency
XVIII	2995	13.1.85	0.88×10^6	8
XIX	3093	22.2.85	0.64×10^6	9
XX	3159	4.4.85	0.93×10^6	8
XXI	3199	13.5.85	0.94×10^6	8
	3205	13.5.85	0.94×10^6	8
XXII	3142	19.6.85	0.94×10^6	8
XXIII	3367	26.7.85	0.63×10^6	9

SEPT. 11, 1986

CDRI PRIMATE ANTIMALARIAL STUDY

Table 1. Serial passages of sporozoite induced P.cynomolgi B infection

Sporozoite passage No.	Monkey Number	Date of inoculation	Sporozoite inoculum (i.v.)	Day of patency
XXIII	3367	26. 7. 85	0.63×10^6	9
XXIV	3456	3. 9. 85	0.76×10^6	9
XXV	3501	6.10. 85	0.92×10^6	8
XXVI	3556	15.11. 85	0.92×10^6	8
XXVII	3611	23.12. 85	0.86×10^6	9
	3614	23.12. 85	0.86×10^6	9
XXVIII	3685	30. 1. 86	0.86×10^6	9
	3705	1. 2. 86	0.72×10^6	8
XXIX	3810	13. 3. 86	0.86×10^6	8
	3812	13. 3. 86	0.88×10^6	8
XXX	3918	25. 4. 86	2.3×10^4	13
	3923	25. 4. 86	2.3×10^4	12
XXXI	3990	4. 6. 86	1.4×10^6	8
	3982	4. 6. 86	1.4×10^6	8
XXXII	4059	9. 7. 86	0.5×10^6	9
	4087	9. 7. 86	0.5×10^6	9
XXXIII	3194	18. 8. 86	0.96×10^6	8

Date: April 15, 1987

CDRI PRIMATE ANTIMALARIAL STUDY

Table: Serial Passages of sporozoite induced *Plasmodium cynomolgi* B infection:

Sporozoite Passage No	Monkey Number	Date of inoculation	Sporozoite inoculum (i.v.)	Day of patency
XXXIII	3194	18.8.86	0.96×10^6	8
	3198	25.8.86	0.84×10^6	8
XXXIV	4243	1.10.86	1.20×10^6	8
	4248	1.10.86	1.20×10^6	8
XXXV	4351	6.11.86	1.6×10^6	8
	4345	6.11.86	5×10^4	11
XXXVI	4245	15.12.86	0.5×10^6	9
	4246	15.12.86	0.5×10^6	10
XXXVII	4406	23.1.87	1.25×10^6	8
	4411	23.1.87	1.25×10^6	8
XXXVIII	4474	5.3.87	0.84×10^6	8
	4475	5.3.87	0.84×10^6	8

PROGRESS REPORT OF THE JOINT COLLABORATIVE PROJECT NO. D.AMD 17-82-G-9515 "Synthesisand screening of New Antimalarial drugs"

Collaboration Institutions :

1. Central Drug Research Institute, (CDRI) Lucknow, (India)
2. Walter Reed Army Institute of Research, Washington, D.C. (U.S.A.) (WRAIR).

Period of Report : September 15, 1982 - April 15, 1987.

Phase IV SCREENING OF CANDIDATE DRUGS

The WRAIR - CDRI collaborative project "Synthesis and screening of New Antimalarial drugs" initiated in Sept. 1982, was aimed at establishing reproducible test systems for blood schizontocidal, radical curative (anti-relapse) efficacy and causal prophylactic screening of new synthetic compounds developed over the years by the US Army Antimalarial Drug Programme and by CDRI and for selection of active compounds for preclinical toxicity studies. Comprehensive protocols have been developed for antimalarial efficacy tests:

Protocol 1. Rhesus blood schizontocidal test.

Protocol 2. Rhesus radical curative test (anti-relapse).

Protocol 3. Rhesus prophylactic test

Protocol 4. Cyclical passage of P.cynomolgi B;

These protocols have been described in detail separately in Annexure "Standardization of screening test systems at CDRI".

The results of the evaluation of new candidate drugs screened under the programme are described below :

A: SCREENING OF RADICAL CURATIVE (ANTI RELAPSE) CANDIDATE DRUGS:

A total of 31 synthetic compounds have been evaluated for radical curative test using 7 day treatment schedule in sporozoite induced P.cynomolgi B- rhesus monkey model. Primaquine, used as reference drug, has been consistently found to be curative at 1.00 mg (base)/kg x 7 day dose. Chloroquine @ 5.0 mg base/kg was always administered as the companion blood schizontocidal drug.

1) WR199507: RCGJM 53. (5-hydroxy-primaquine)

This compound was tested at 2.0 mg/kg dose in two monkeys (No.2356, 2357) and both of them were radically cured.

2). RCGJM 33 : (5,6-dimethoxy-8-aminoquinoline)

This compound was inactive at 1.58 mg/kg x 7 days in two monkeys (No.2337, 2338). Both the monkeys relapsed on day 15 and 16 respectively.

3). CDRI 83/472: (6-methoxy-8-aminoquinoline): WR 15081.

This compound was inactive at 135 mg/kg x 7 days in two monkeys (No.2235, 2236). Both the monkeys relapsed on day 17 and 14 respectively.

4). RCGJM 161 (6-hydroxy-8-aminoquinoline)

This compound was inactive at 2.36 mg/kg x 7 days in two monkeys (No.2237, 2238). Both the monkeys relapsed on day 17.

5). CDRI 83/383 (N-galactosido-primaquine)

Two preparations of this compound (a.Amorphous, b.Crystalline) have been tested for radical curative activity.

a). Amorphous preparation : was tested in first experiment at 3.25 mg/kg x 7 days in two monkeys (no.2279, 2280), at 1.62 mg/kg x 7 days in two monkeys (no.2204, 2205) and at 0.82 mg/kg in one monkey (No.2203). All the five monkeys including the one at 0.82 mg/kg, were cured. However, in the second experiment five monkeys (no.2321, 2346, 2377, 2376, 2379) were tested at the above dose (0.82 mg/kg), and all the five monkeys relapsed on day 23, 24, 41, 53 and 16 respectively. The lower doses 0.51 mg/kg and 0.41 mg/kg tested in two monkeys each were inactive.

b). Crystalline preparation : was tested at 0.82 mg/kg and 0.41 mg/kg x 7 days in two monkeys each. The dose of 0.82 mg/kg was curative in monkey No.2361 and 2369 and the lower dose 0.41 mg/kg was inactive in two monkeys (No.2367, 2368). The effective dose 0.82 mg/kg corresponds to 0.50 mg/kg primaquine base.

6). CDRI 83/382 (N-glucosido-primaquine)

This compound was tested in three experiments. A dose of 0.82 mg/kg x 7 days of N -glucosido-primaquine (containing 0.5 mg/kg primaquine base) was curative in 8 monkeys (expt. I - No.2390, 2391,2393, 2397 and 2398, and Expt. II, No.2535, 2536 and 2537). The lower dose 0.41 mg/kg was tested in 11 monkeys, out of which 3 monkeys (No.2360, 2366 and 2449) were successfully

cured and the remaining 8 monkeys relapsed between day 21- 77. Three monkeys at 0.20 mg/kg also relapsed between day 14-22. Revalidation studies at 0.8 mg/kg dose with a newbatch of this compound in 3 monkeys showed that one of the monkeys relapsed on day 22, while other two were cured.

7. CDRI 84/136. (N-mannosido-primaquine)

This compound was tested at 1.62 mg/kg x 7 days in two monkeys (no.2353 and 2289) and at 0.80 mg/kg in three monkeys (no.2714, 2723 and 2724). Both these doses were curative. The lower dose of 0.80 mg/kg corresponds to 0.50 mg/kg primaquine base. Further studies were conducted with three monkeys at 0.8 mg/kg and 4 monkeys at 0.4 mg/kg dose level. All the four monkeys at lower dose relapsed on day 13, 13, 16 and 16 and one of the three monkeys at 0.8 mg/kg relapsed on day 35. The other two monkeys were cured.

8. CDRI 84/137 (N-glucosido-6-methoxy-8-amino-quinoline) -

This compound was tested at 5.0 mg/kg in two monkeys (no.2330 and 2283) and the monkeys relapsed on day 14 and 15.

9. CDRI- RCG9 (Bromoprimaquine)

This compound was tested at 3.16 mg/kg and 1.00 mg/kg x 7 days, in two monkeys at each dose level. Both the doses were inactive.

19) WR 242511

The compound was tested in Ist experiment at 4 dose levels x 7 days (1.0 mg/kg; 0.316 mg/kg, 0.10 mg/kg and 0.0316 mg/kg dose

levels in three monkeys each). Doses of 1.0, 0.316 and 0.10 mg/kg were fully curative. At 0.0316 mg/kg dose, however, two monkeys (no.2321, 2382) were radically cured, while the 3rd monkey (no.2384) showed a relapse on day 51.

In the second experiment, five monkeys were tested at each of thd 3 dose levels (0.316 mg/kg; 0.10 mg/kg and 0.0316 mg/kg x 7 days). All the three dose levels were curative.

Follow up studies were carried out using 3 monkeys at 0.1 mg/kg and 4 monkeys each at 0.0316 mg/kg and 0.010 mg/kg dose levels . The curative efficacy of 0.1 mg/kg dose has been re-validated as all the three monkeys in present study were also protected. However, four monkeys at 0.0316 mg/kg relapsed on day 13, 14, 14 and 15, and four monkeys at 0.010 mg/kg also relapsed on day 12, 13, 18 and 15. This compound was sent as reference for validation of our test system and our results show that the primaquine index of the compound seems to be 10.

11). WR 249252

This compound was tested at 4 dose levels x 7 days (1.0mg/kg; 0.316 mg/kg, 0.10 mg/kg and 0.0316 mg/kg, in two monkeys at each dose). The compound was curative at 1.0 and 0.316 mg/kg dose levels. At 0.10 and 0.0316 mg/kg doses, the treated monkeys showed relapse. Monkeys at 0.10 mg/kg relapsed on day 23 and 60, and those at 0.0316 mg/kg relapsed on day 14 and 15). Revalidation studies with 4 monkeys at 1.00 mg/kg, 5 monkeys at 0.316 mg/kg and 4 monkeys at 0.10 mg/kg showed that all the monkeys treated at 1.00 mg/kg and 0.316 mg/kg doses were cured. One of the three monkeys at 0.10mg/kg dose relapsed on day 19 while the other three monkeys did not relapse during observation

period.

12. CDRI 80/53: This compound has shown radical curative activity at 1.25 mg/kg dose in 8 monkeys and at 2.5 mg/kg in 5 monkeys. The curative dose of 1.25 mg/kg was again revalidated in 5 monkeys and all the monkeys were cured. This compound has also shown radical curative activity at 2.92 mg/kg x 3 days in 6/7 monkeys.

Met Hb toxicity of this compound is 3-4 times lower than primaquine as shown by beagle dog model. Further this compound has been found to be safe in 3 months sub-acute toxicity tests in rats and monkeys.

13. Compound CDRI 83/302: was tested at 4.0 mg/kg x 7 days in two monkeys. The compound was inactive as both the monkeys showed relapse on day 12 and 15 respectively.

14. Compound CDRI 83/303: was tested at 4.0 mg/kg x 7 days in three monkeys. The compound was inactive as all the three monkeys showed relapse on day 10, 10 and 11 respectively.

15. Compound CDRI 85/41: was tested at 1.00 mg/kg in three monkeys. Two monkeys developed patency at days 26 and 39, while one monkey has shown no relapse till 90 days of observation.

16. Compound CDRI 85/185: was tested at 1.78 mg/kg x 7 days in four monkeys, and all the four monkeys showed relapse on day 13, 13, 15 and 34 respectively.

17. Compound CDRI 85/276 was tested at 3.16 mg/kg x 7 days in 3 monkeys and at 1.00 mg/kg x 7 days in 2 monkeys. All the 5 monkeys at both dose levels, were cured. In the 2nd experiment, 3/3 monkeys at 1.00 mg/kg and 3/3 monkeys at 0.316 mg/kg were cured.

18. Compound 85/277 was tested in three monkeys each at 3.16 mg/kg, 1.00 mg/kg and 0.316 mg/kg dose levels. All the 3 monkeys at both 3.16 mg/kg and 1.00 mg/kg and 2/3 monkeys at 0.316 mg/kg were cured ,while the third monkey at the lowest dose relapsed on day 45. Revalidation studies showed that 3/3 monkeys at 1.00 mg/kg dose were again cured while all the three monkeys at 0.316 mg/kg dose relapsed on day 18, 19 and 28.

19. Compound 85/403: was tested in 3 monkeys each at 3.16 mg/kg, 1.00 mg/kg and 0.316 mg/kg dose levels. All the three monkeys at both 3.16 mg/kg and 1.00 mg/kg and 1/3 monkeys at 0.316 mg/kg were cured. Two monkeys at the lowest dose relapsed on days 25 and 34.

20. Compound 85/278 was tested in 3 monkeys each at 1.00 mg/kg, 0.316 mg/kg and 0.10 mg/kg dose levels. Two of the 3 monkeys at 1.0 mg/kg were cured, while third relapsed on day 29. At 0.310 mg/kg dose, one monkey was cured and other two relapsed on May 22. At 0.10 mg/kg dose all the three monkeys relapsed on day 10, 21 and 79.

21. Compound CDRI 85/285. was tested in 3 monkeys each at 1.00 mg/kg, 0.316 mg/kg and 0.10 mg/kg dose levels. All the three monkeys at 1.00 mg/kg dose were cured. Three monkeys at 0.316 mg/kg relapsed on day 15, 17 and 25. Two of the

three monkeys at 0.10 mg/kg dose relapsed on day 12 and 15, while the third monkey did not show any relapse till day 90. During 2nd experiment, 3/3 monkeys at 1.00 mg/kg and 2/2 monkeys at 0.316 mg/kg were cured.

22. Compound CDRI 86/5 : was tested in two monkeys each at 3.16 mg/kg, 1.00 mg/kg and 0.316 mg/kg dose levels. All the four monkeys at 3.16 mg/kg and 1.00 mg/kg were cured. Two monkeys at the lowest dose 0.316 mg/kg relapsed on day 22 and 27.

23. Compound CDRI 86/4 : was tested in two monkeys each at 1.00 mg/kg and 0.316 mg/kg dose levels and both the doses were curative as none of the four monkeys relapsed during observation period. During validation of curative dose, 2/2 monkeys at 1.00 mg/kg and 2/3 monkeys at 0.316 mg/kg were cured. One monkey at 0.316 mg/kg relapsed on day 59. One out of two monkeys at lowest dose of 0.10 mg/kg relapsed on day 12, while other was cured.

24. Compound 86/216 was tested in two monkeys at 3.16 mg/kg and 1.00 mg/kg dose levels. Both the doses were non-curative as monkeys at 3.16 mg/kg relapsed on day 15 and 18 and monkeys at 1.00 mg/kg relapsed on day 14 and 22.

25. Compound 86/217 was tested in 3 monkeys at 3.16 mg/kg dose and all the 3 monkeys relapsed on day 14, 15 and 15 respectively.

26. Compound WR 254715 was tested in two monkeys each at 1.00 mg/kg and 0.316 mg/kg and all the four monkeys were cured. In the 2nd experiment this compound was tested in two monkeys

each at 0.316 mg/kg and 0.10 mg/kg doses. Both monkeys at 0.316 mg/kg and 1/2 monkey at 0.10 mg /kg was cured while other monkey at lower dose relapsed on day 46.

27. Compound WR 254763 was tested in two monkeys each at 1.00 mg/kg and 0.316 mg/kg dose levels and all the four monkeys were cured. In the repeat experiment, two monkeys at 0.316 mg/kg were cured while two monkeys at lower dose of 0.10 mg/kg relapsed on day 36 and 50.

28 Compound CDRI 86/6: was tested in 3 monkeys at 1.00 mg/kg and in 2 monkeys at 0.316 mg/kg dose. Both the doses were curative as none of the 5 monkeys showed any relapse during the observation period.

29. Compound CDRI 86/7 was tested in 3 monkeys at 1.00 mg/kg and in 2 monkeys at 0.316 mg/kg. Both monkeys at lower dose of 0.316 mg/kg relapsed on day 12, and 13. Two of the three monkeys at 1.00 mg/kg dose relapsed on day 12 and 20 while the third monkey was cured.

30. Compound WR 238605 was tested in two monkeys at 0.316 mg/kg dose x 7 days. Both the monkeys remained negative till day 100 after the end of treatment. This compound was also tested in a single dose regimen. Three monkeys treated at 2.212 mg/kg single dose(= 0.316x7) did not show any relapse till day 100 and were cured.

31. Compound WR 197236 was tested in two monkeys at 10.0 mg/kg dose; one of the treated monkey (No.4348) relapsed on day 95 after end of treatment while other monkey was cured.

B. Screening of candidate drugs for causal prophylactic activity.

A total of 23 synthetic compounds have been evaluated for causal prophylactic activity using sporozoite induced infections of P.cynomolgi B in rhesus monkeys in either 9 day treatment schedule/ three day treatment schedule/ single dose bioassay studies. The curative doses of primaquine (base) used as the reference drug were established as follows :

a) 9-day treatment schedule

Primaquine 1.00 mg/kg x 9 days

b) 3-Day treatment schedule.

Primaquine 1.78 mg/kg x 3 Days. Most of the candidate drugs have been screened using 3-day schedule.

c) Single dose Bioassay.

Primaquine 5.34 mg/kg x 1 dose on day 0.

1) RCGJH 52 (5-methoxyprimaquine)

This compound showed causal prophylactic activity at 2.23 and 1.11 mg/kg dose x 9 days in two monkeys each.

2) WR199507; RCGJM 53 (5-hydroxyprimaquine)

The compound was toxic after 2 doses at 2.12 mg/kg after intravenous administration, but at 1.06 mg/kg dose x 9 days by oral route, the compound was inactive. when tested in 3 day treatment schedule; the compound was inactive at 10.0, 3.16; 1.00 and 0.316 mg/kg doses in two monkeys each.

3). WR250016/ RCGJM 55 (5-hydroxy-6-desmethylprimaquine)

The compound was inactive in 2 monkeys at 2.01 mg/kg x 9 day dose by intravenous route. The compound was also inactive when tested orally at 4 dose levels (10.0, 3.16, 1.00 and 0.316 mg/kg x 3 days) in two monkeys each.

4). CDRI 83/472;WR 15081 (6-methoxy-8-aminoquinoline)

The compound was inactive in 2 monkeys at 1.35 mg/kg x 9 day dose by intravenous route. The compound was also inactive when tested orally at 4 dose levels (10.0, 3.16, 1.00 and 0.316 mg/kg x 3days) in two monkeys each.

5). RCGJM-33 (5,6-dimethoxy-8-aminoquinoline)

The compound was tested at 1.58 mg/kg x 9 days by both intravenous/oral routes in the two monkeys each, and was found to be inactive.

6). RCGJM 162 (5-hydroxy-6-methoxy-8-aminoquinoline).

This compound at 2.94 mg/kg dose was toxic in two monkeys after intravenous administration whereas at 1.47 mg/kg dose x 9 days it was inactive in two monkeys by oral route.

7). WR6890; RCGJM 161 (6-hydroxy-8-aminoquinoline)

This compound at 2.36 mg/kg dose x 9 days was inactive in two monkeys by intravenous route. In the three day treatment schedule via oral route, this compound was curative in 2 monkeys at 10.0 mg/kg dose while lower doses of 3.16, 1.00 and 0.316 mg/kg in two monkeys each were inactive.

8). CDRI 83/383 (N-galactosidoprimaquine)

This compound was tested in two monkeys each at three dose levels (3.25, 1.62 and 0.51 mg/kg x 9 days) by oral route and it was found to be active at all the three dose levels.

9). CDRI 83/382 (N-glucosidoprimaquine)

This compound was tested at three dose levels (four monkeys at3.25, two monkeys at 1.62 and two monkeys at 0.51 mg/kgx 9 days) by oral route, and it was found to be active at all the three dose levels.

10). WR 242511

The compound was tested orally in two experiments. In Expt.I, four, dose levels (1.78, 1.00, 0.316, 0.10 mg/kg x 3 days) were tested by oral administration in two monkeys at each dose level. All the four doses were found to be curative. In Expt.II, three dose levels were tested i.e. two monkeys at 0.316 mg/kg, five monkeys at 0.10 mg/kg, and two monkeys at 0.0316 mg/kg x 3 days. The doses of 0.316 and 0.10 mg/kg were consistently curative. However, the lowest dose (0.0316 mg/kg) was inactive.

Since this compound had been found to be active at 0.1 mg/kg dose in the three day model, its activity in single dose bioassay was also studied. In the Ist experiment, this compound was administered at 0.30 mg/kg (single dose) to two monkeys each on day -2 or -1 or day 0. However, none of the monkeys was protected and all the six monkeys became patent between day 9-14. In the 2nd experiment, two monkeys each

were treated at 0.95 mg/kg (single dose) on day -5 or -3 or day 0. While both the monkeys treated on day 0 were protected after challenge infection, the remaining four monkeys treated either on day -3 or -5, became patent between day 10-11.

WR 225448.

The compound was tested orally at 4 dose levels (1.78, 1.00, 0.316 and 0.10 mg/kg x 3 days) in two monkeys each. All the doses were curative.

In the revalidation studies, the compound was tested in 5 monkeys each at 0.316 mg/kg, 0.1 mg/kg and 0.316 mg/kg dose levels. ~~All the five monkeys at highest dose of 0.316 mg/kg dose levels.~~ All the five monkeys at highest dose of 0.316 mg/kg were protected. Four of the five monkeys tested at 0.1 mg/kg became patent on day 15, 16, 16 and 20, while one monkey was protected at this dose. At the lowest dose of 0.0316 mg/kg, four monkeys became patent on day 12, 13, 14 and 24 and one monkey was cured.

This compound has been found to be active at 0.316 mg/kg dose in the three day treatment schedule. For single dose bioassay, this compound was administered at 2.84 mg/kg dose (= 0.316 x 9) to two monkeys each on day -5 or -3 or day 0. The results showed that after sporozoite inoculation on day 0, monkeys administered compound on day 0 or -3 were protected while two monkeys treated on day -5 became patent on day 13 and 17.

12. WR 238605.

The compound was tested orally at 4 dose levels (1.78, 1.00, 0.316 and 0.10 mg/kg x 3 days) in two monkeys each. The doses of 1.78, 1.00 and 0.316 mg/kg were found to be effective, while one of the two monkeys at 0.10 mg/kg dose became patent. Revalidation studies have shown curative action at 0.316 mg/kg in 5 monkeys, while the lower ~~doses (0.1 mg/kg and 0.0316 mg/kg in 5 monkeys, while the lower~~ doses (0.1 mg/kg and 0.0316 mg/kg) were inactive in 5 monkeys each.

This compound has been found to be active at 0.316 mg/kg dose level in the 3 day treatment schedule. For the single dose bioassay, in the first experiment, this compound was administered to two monkeys each at 0.948 mg/kg single dose on either day -2 or -1 or 0 of sporozoite inoculation. One of the two monkeys administered drug on day 0 was cured while remaining 5 monkeys became patent between day 10-12. In the second experiment, with fresh sample of the compound, two monkeys each were administered this compound at 2.84 mg/kg single dose on day -5 or -3 or 0. Both the monkeys treated on day 0, and 1 of the 2 monkeys treated on day -3 were protected, the other monkey treated on day -3 became patent on day 16 and two monkeys treated on day -5 were patent on day 11 and 14.

13. CDRI. RCG 9 (Bromoprimaquine)

The compound has been tested orally at two dose levels (3.16 and 1.00 mg/kg x 3 days) and it has shown activity in one of the two monkeys at 3.16 mg/kg dose, while the lower

dose (1.00 mg/kg) was inactive.

14. WR 249420: Was tested at 1.78, 1.00, 0.316 and 0.10 mg/kg x 3 day dose level, employing 2 monkeys for each dose. All the monkeys at doses 0.10 to 1.78 mg/kg were cured as no patency was recorded upto observation period of 70 days. In the 2nd experiment two monkeys were treated at each of the three dose levels. i.e. 0.316 mg/kg, 0.10 mg/kg and 0.0316 mg/kg. Both the monkeys at 0.316 mg/kg were cured while the monkeys at 0.1 mg/kg became patent on day 12 and 14 and those at 0.0316 mg/kg became patent on day 9 and 10.

15. WR 7295 : was tested in two monkeys each, at dose level of 10.0, 3.16 and 1.00 mg/kg. None of these doses was curative.

16. WR 93133 : was tested in two monkeys each at 10.0, 3.16 and 1.00 mg/kg dose levels. None of these doses was curative.

17. WR 194905: was tested in two monkeys each at 10.0, 3.16 and 1.00 mg/kg dose levels. None of these doses was curative.

18. WR 190729: was tested in two monkeys each at 10.0, 3.16 and 1.00 mg/kg dose levels. None of these doses was curative.

19. WR 158124: was tested at 10.0, 3.16 and 1.00 mg/kg in 2 monkeys wach. None of the doses was curative.

20. WR 214235: was tested at 3.16 and 1.0 mg/kg in 2 monkeys each. None of the doses was curative.

21. Compound WR 226626: was tested in two monkeys each at 10.0 mg/kg, 3.16 mg/kg and 1.00 mg/kg dose levels. None of the these doses were curative as all the monkeys at 3 dose levels became patent on day 9 or 10.

22. Compound WR 249252: was tested in two monkeys each at 0.316 mg/kg, 0.10 mg/kg and 0.0316 mg/kg dose levels. Monkeys at 0.316 mg/kg dose became patent on day 14 and 19, those at 0.10 mg/kg became patent on day 11, and two monkeys at 0.0316 mg/kg became patent on day 9 and 10.

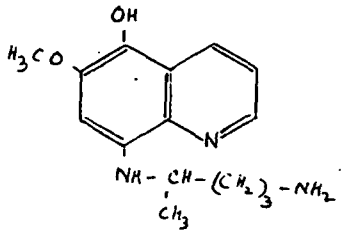
23. Compound WR 197236: was tested in two monkeys each at 31.6 mg/kg and 10.0 mg/kg dose levels. Both the monkeys at 31.6 mg/kg were cured while monkeys at 10.0 mg/kg dose were patent on day 12 and 33.

Table: Summary of the results of Radical curative activity of primaquine against sporozoite induced infection of *P. cynomolgi* B in rhesus monkeys.

Dose mg/kg	No. of monkeys Protected/Treated	Relapse on day
0.18	0/2	10,10
0.316	0/2	18,28
0.56	6/6	Cured
1.00	30/30	Cured
1.30	7/7	Cured
3.16	2/2	Cured
10.00	2/2	Cured

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 199507 (=ROGUE 53)



SN:

DATE REC'D: OCT. 1958

QUANTITY:

VEHICLE: METHYL CELLULOSE

ROUTE: ORAL

RADICAL CURATIVE TEST

DOSE (mg/kg) (Base)	MONKEY NO.		RESULT
2.0	2353	No relapse till day	100
2.0	2357	No relapse till day	100

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

XR: RCGJm 33

BN:

DATE REC'D: Oct. 1983

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

RADICAL CURATIVE TEST

DOSE (mg/kg)(base)	MONKEY #	RESULT
1.58	2337	Relapse on day 15
1.58	2338	Relapse on day 16

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 83/472 (= WR 15081)

BN:

DATE REC'D:

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

RADICAL CURATIVE TEST

DOSE (mg/kg)(base)	MONKEY #	RESULT
1.35	2235	Relapse on day 17
1.35	2236	Relapse on day 14

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: RCGJM 161

BN:

DATE REC'D: Oct. 1983

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

RADICAL CURATIVE TEST

DOSE (mg/kg)(base)	MONKEY #		RESUL
2.36	2237	Relapse on day 17	
2.36	2238	Relapse on day 17	

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

VR: CDRI 83/353 (Amorphous)

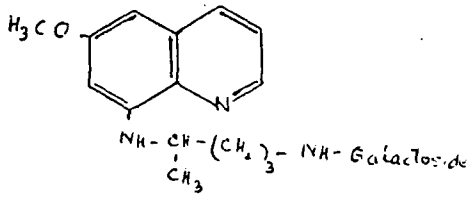
BN:

DATE REC'D:

QUANTITY:

VEHICLE: METHYL CELLULOSE

ROUTE: ORAL



RADICAL CURATIVE TEST

DOSE (mg/kg) (Base)	MONKEY NO.	RESULT
EXPT.I 3.25	2379	No relapse till day 100
3.25	2380	No relapse till day 100
1.62	2384	No relapse till day 100
1.62	2386	No relapse till day 100
0.82	2383	No relapse till day 100
0.51	2383	Relapse on day 45
0.51	2384	Relapse on day 67
EXPT.II.0.82	2321	Relapse on day 23
0.82	2346	Relapse on day 24
0.82	2377	Relapse on day 14
0.82	2378	Relapse on day 50
0.82	2379	Relapse on day 10
0.41	2331	Relapse on day 14
0.41	2332	Relapse on day 14

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 83/383 Crystalline

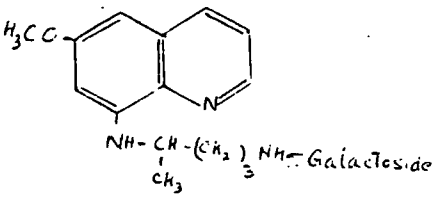
I.N:

ATE REC'D:

QUANTITY:

VEHICLE: METHYL CELLULOSE

ROUTE: ORAL



RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
0.82	2361	No relapse till day 100
0.82	2369	No relapse till day 100
0.41	2367	Relapse on day 25
0.41	2368	Relapse on day 25

Note: 0.82 mg/kg base is equivalent to 0.50 mg/kg primaquine base.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: CDRI 83/382

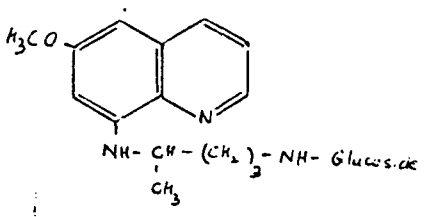
BN:

DATE REC'D:

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: oral

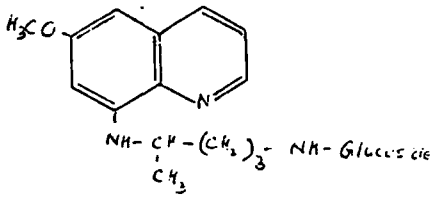


RADICAL CURATIVE TEST

	DOSE (mg/kg) (base)	MONKEY NO.	RESULT
[illegible] T.I.	0.82	2390	No relapse till day 100
	0.82	2391	No relapse till day 100
	0.82	2393	No relapse till day 100
	0.82	2397	No relapse till day 100
	0.82	2398	No relapse till day 100
	0.41	2360	No relapse till day 100
	0.41	2365	Relapse on day 48
	0.41	2366	No relapse till day 100
[illegible] T.II.	0.41	2446	Relapse on day 32
	0.41	2447	Relapse on day 77
	0.41	2448	Relapse on day 21
	0.41	2449	No relapse till day 100
	0.41	2451	Relapse on day 7[illegible]
[illegible] T.III.	0.82	2535	No relapse till [illegible]
	0.82	2531	No relapse till [illegible]

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 83/362 (Contd.)



IN:

ATE REC'D:

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.		RESULT
0.41	2349	Relapse on day 36	
0.41	2351	Relapse on day 53	
0.41	2352	Relapse on day 40	
0.20	2358	Relapse on day 19	
0.20	2529	Relapse on day 22	
0.20	2539	Relapse on day 14	

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

SEPT. 11, 1968

(Page 20)

(Revalidation results)

WR#= CDRI 83/382

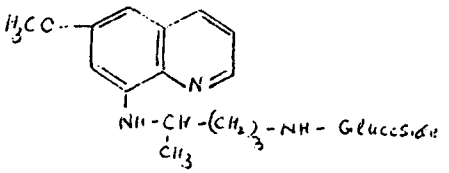
BN: II

DATE REC'D: 17-2-66

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: oral



RADICAL CURATIVE TEST(7 day treatment)

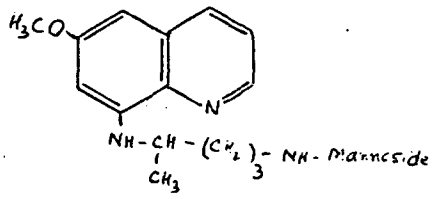
DOSE (mg/kg) base *	MONKEY #	RESULT
0.6	3698	Relapse on day 22
0.3	3704	Cured
0.8	3740	Cured

*Chloroquine 0.5 mg/kg (base) x 7 days was used asthe companion drug.

0.8 mg/kg of the compound (primaquine glucoside) is equal to 0.5 mg/kg primaquine base.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 84/136 (Primaquine mannoside)



I.N:

DATE REC'D: May, 1984

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
1.62	2353	No relapse till day 100
1.62	2289	No relapse till day 100
0.80	2714	No relapse till day 100
0.80	2723	No relapse till day 100
0.80	2724	No relapse till day 100.

Note: 0.80 mg/kg base is equivalent to 1.30 mg/kg primaquine base.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 84/136 (revalidation)

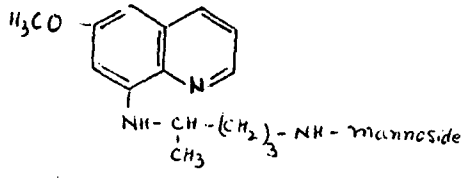
BN: IInd

DATE REC'D: 14-6-1985

QUANTITY: 200 mg.

VEHICLE: Methyl cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY	RESULT
0.80	3215	Relapse on day 35
0.80	3284	Cured
0.80	3195	Cured
0.40	3213	Relapse on day 16
0.40	3214	Relapse on day 13
0.40	3218	Relapse on day 16
0.40	3221	Relapse on day 13

*Chloroquine @ 5 mg/kg base x 7 days was used as companion drug.

0.80 mg/kg of the compound (Primaquine mannoside) is equal to 0.5 mg/kg primaquine base.

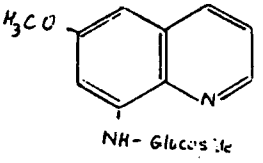
CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 84/137

BN:

DATE REC'D:

QUANTITY:



VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
5.0	2330	Relapse on day 15
5.0	2383	Relapse on day 14

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI RCG 9 (Bromo-primaquine)

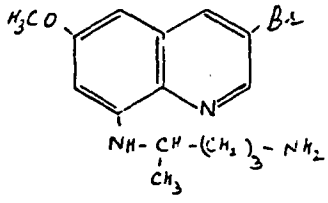
I.S:

DATE REC'D: SEPT. 1984

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.		RESULT
3.16	2776	Relapse on day 27	
3.16	2779	Relapse on day 17	
1.00	2780	Relapse on day 29	
1.00	2781	Relapse on day 14	

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 342511

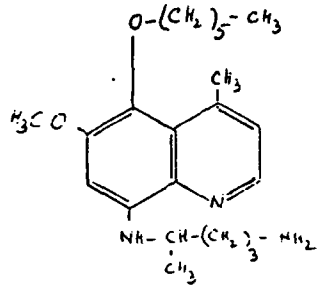
N: BJ 78592

ATE REC'D: Dec. 1982

QUANTITY: 2 gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
1.0	2367	No relapse till day 100
1.0	2368	No relapse till day 100
1.0	2385	No relapse till day 100
0.316	2346	No relapse till day 100
0.316	2380	No relapse till day 100
0.316	2401	No relapse till day 100
0.10	2379	No relapse till day 100
0.10	2383	No relapse till day 100
0.10	2400	No relapse till day 100
0.0316	2321	No relapse till day 100
0.0316	2382	No relapse till day 100
0.0316	2381	Relapse on day 81

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 242511 (Revalidation results)

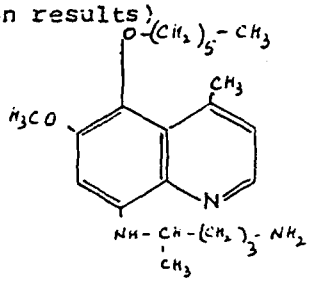
BN: [illegible] 70892

DATE REC'D: DEC. 1982

QUANTITY: 2 gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
EXPT. II 0.316	2508	No relapse till day 100
0.316	2510	No relapse till day 100
0.316	2511	No relapse till day 100
0.316	2513	No relapse till day 100
0.316	2514	No relapse till day 100
0.10	2516	No relapse till day 100
0.10	2517	No relapse till day 100
0.10	2518	No relapse till day 100
0.10	2519	No relapse till day 100
0.10	2520	No relapse till day 100
0.0316	2521	No relapse till day 100
0.0316	2522	No relapse till day 100
0.0316	2510	No relapse till day 100
0.0316	[illegible]	No relapse till day [illegible]
0.0316	[illegible]	No relapse till day [illegible]

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

(Revalidation results)

WR: 242511

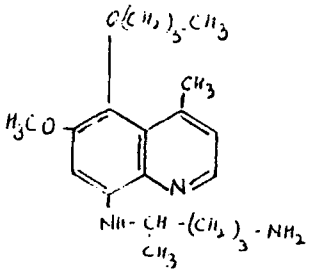
BN: 78592

DATE REC'D: DEC. 1982

QUANTITY: 2 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base*	MONKEY	RESULT
0.10	3758	Cured
0.10	3767	Cured
0.10	3826	Cured
0.0316	3821	Relapse on day 14
0.0316	3823	Relapse on day 15
0.0316	3829	Relapse on day 13
0.0316	3764	Relapse on day 14
0.010	3822	Relapse on day 13
0.010	3825	Relapse on day 15
0.010	3828	Relapse on day 13
0.010	3766	Relapse on day 12

*Chloroquine @ 5 mg/kg base x 7 day was used as the companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 249252

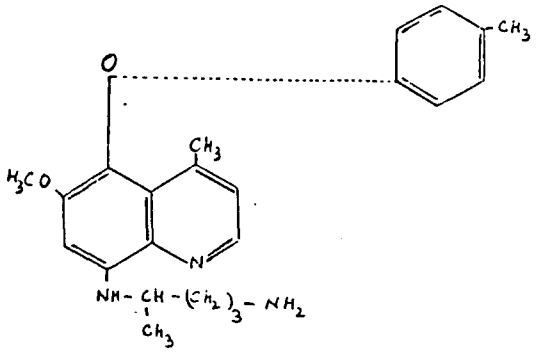
: BJ 76305

TE REC'D: Dec. 1982

QUANTITY. 2 gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST

DOSE (mg/kg) (Base)	MONKEY NO.	RESULT
1.0	2[illegible]	No relapse till day 100
1.0	2101	No relapse till day 100
0.316	2304	No relapse till day 100
0.316	2306	No relapse till day 100
0.10	2320	Relapse on day 60
0.10	2322	Relapse on day 23
0.0316	2330	Relapse on day 14
0.0316	2333	Relapse on day 15

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

(Revalidation results)

WR: 249252

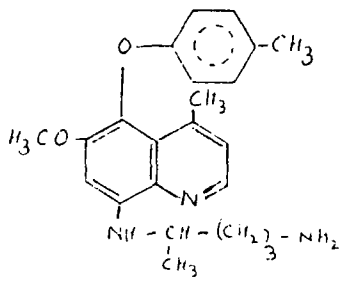
BN: EJ 76365

DATE REC'D: DEC. 1982

QUANTITY: 2 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base*	MONKEY	RESULT
1.00	3280	Cured
1.00	3282	Cured
1.00	3372	Cured
1.00	3507	Cured
0.316	3201	Cured
0.316	3363	Cured
0.316	3364	Cured
0.316	3382	Cured
0.316	3383	Cured
0.10	3263	Cured
0.10	3267	Relapse on day 19
.10	3336	Cured
0.10	3367	Cured

*Chloroquine 0.5 mg/kg (base) x 7 days was used as the comparison drug

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 80/53 (Revalidation)

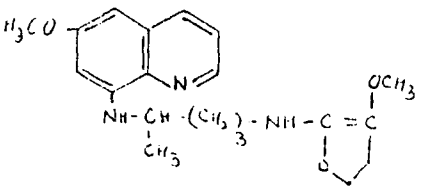
BN: Batch II

DATE REC'D: 15.6. 1985

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY	RESULT
1.25	3333	Cured
1.25	3336	Cured
1.25	3339	Cured
1.25	3351	Cured
1.25	3356	Cured

*Chloroquine 4.5 mg/kg base x 7 days was used as companion drug.

Date: April 1
1987

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 80/53

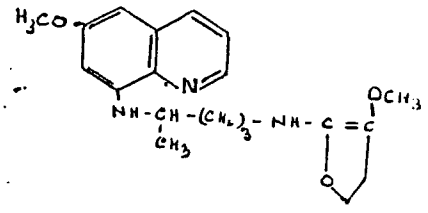
BN: IIIrd

DATE REC'D:

QUANTITY: 2 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TESTING

DOSE (mg/kg)	MONKEY #	RESULT
8.75 x 1 day	3983	Relapse on day 24
8.75 x 1 day	3986	Cured
8.75 x 1 day	4000	Relapse on day 22
8.75 x 1 day	4042	Relapse on day 24
8.75 x 1 day	4085	Relapse on day 81
8.75 x 1 day	4088	Cured
2.92 x 3 day	4001	Cured
2.92 x 3 day	4002	Cured
2.92 x 3 day	4005	Cured
2.92 x 3 day	4078	Cured
2.92 x 3 day	4079	Cured
2.92 x 3 day	4080	Relapse on day 28
2.92 x 3 day	4081	Cured

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 83/302

BN:

DATE REC'D:

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg)	MONKEY #	RESULT
4.0	3091	Relapse on day 12
4.0	3092	Relapse on day 15

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 83/303

BN:

DATE REC'D:

QUANTITY: 500 mg

VEHICLE: Methyl cellulose

ROUTE: Oral

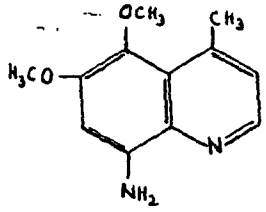
RADICAL CURATIVE TEST

DOSE (mg/kg) base	MONKEY #	RESULT
4.0	3218	Relapse on day 10
4.0	3219	Relapse on day 11
4.0	3221	Relapse on day 10

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI: 85/41

BN: 1. 5,6-Dimethoxy-1-methyl-8-aminoquinoline. $2H_3PO_4$



DATE REC'D: 3.6.1985

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: Oral

RADICAL CURATIVE TEST

DOSE (mg/kg) base	MONKEY #	RESULT
1.00	3286	No relapse till day 90.
1.00	3292	Relapse on day 26
1.00	3302	Relapse on day 39

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

MR: CDRI: 85/185

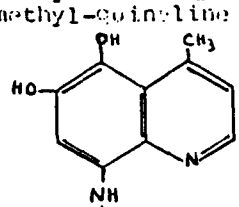
PN: I. 8 (4-amino-1-methyl-butyl amino) 5,6-dihydroxy-4-methyl-quinoline

DATE REC'D: 6-7-1985

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: Oral



$CH_3-CH-CH_2.CH_2.CH_2.NH_2.3HBr.$

Mol.wt: 518

RADICAL CURATIVE TEST

DOSE (mg/kg)	MONKEY #	RESULT
1.78	3337	Relapse on day 13
1.78	3340	Relapse on day 15
1.78	3353	Relapse on day 34
1.78	3354	Relapse on day 13.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

~~NR:~~ CDRI 85/276

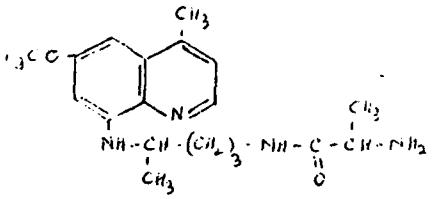
BN: I

DATE REC'D: 10-7-1985

QUANTITY: 600 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY #	RESULT
3.16	3214	Cured
3.16	3219	Cured
3.16	3293	Cured
1.00	3213	Cured
1.00	3218	Cured

* Chloroquine @ 5 mg/kg base x 7 days was used as the companion drug.

Date: 12.1.87.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

CDRI 85/276

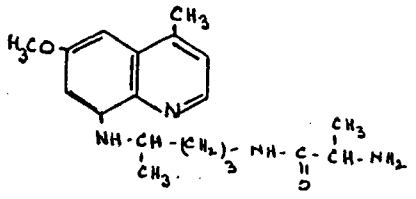
BN: IInd (expt. 2).

DATE REC'D: July, 86.

QUANTITY: 400 mg

VEHICLE: Methyl cellulose

ROUTE: Oral.



RADICAL CURATIVE TESTING (7 day treatment)

DOSE (mg/kg)	MONKEY	RESULT
1.00	3813	Cured
1.00	3816	Cured
1.00	3818	Cured
0.316	4054	Cured
0.316	4057	Cured
0.316	4089	Cured

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

~~NR~~ CDRI 85/277

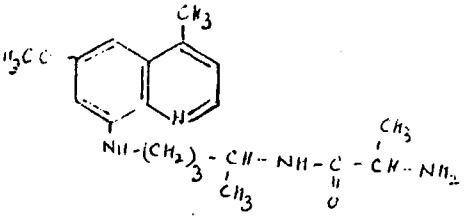
BN: I

DATE REC'D: 30-10-1985

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) *	MONKEY #	RESULT
3.16	3582	Cured
3.16	3583	Cured
3.16	3586	Cured
1.00	3432	Cured
1.00	3475	Cured
1.00	3476	Cured
0.316	3581	Cured
0.316	3590	Relapse on day 45
0.316	3600	Cured

*Chloroquine 0.5 mg base/kg x 7 days was used as companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

Date: 12.1.87.

CDRI 85/277

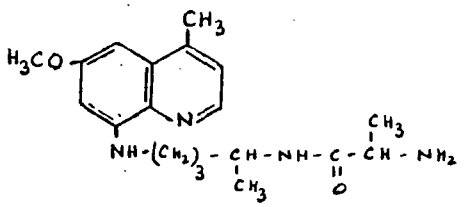
BN: IInd (Expt. 2)

DATE REC'D: July 1986

QUANTITY: 400 mg

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg)	MONKEY #	RESULT
1.00	3993	Cured
1.00	3994	Cured
1.00	4006	Cured
0.316	3987	Relapse on day 28
0.316	3999	Relapse on day 19
0.316	4003	Relapse on day 18

~~WR~~: CDRI 85/403

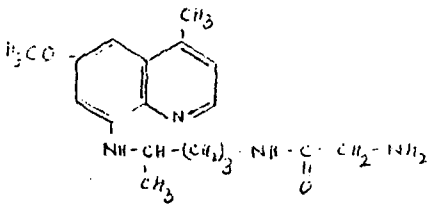
BN: I

DATE REC'D: 30-10-1985

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (3 day treatment)

DOSE (mg/kg) *	MONKEY #	RESULT
3.16	3595	Cured
3.16	3597	Cured
3.16	3601	Cured
1.00	3584	Cured
1.00	3585	Cured
1.00	3589	Cured
0.316	3586	Relapse on day 25
0.316	3587	Relapse on day 34
0.316	3599	Cured

*Chloroquine @ 5 mg base/kg x 7 days was used as companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

NR: CDRI 85/278

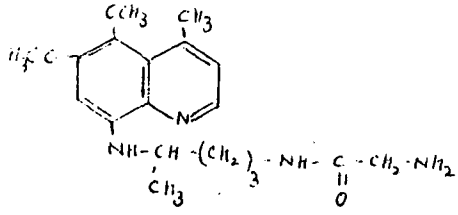
BN: I

DATE REC'D: 31-12-1985

QUANTITY: 500 mg

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base*	MONKEY #	RESULT
1.0	3645	Cured
1.0	3653	Relapse on day 29
1.0	3655	Cured
0.316	3648	Relapse on day 22
0.316	3649	Relapse on day 22
0.316	3660	Cured
0.10	3651	Relapse on day 21
0.10	3652	Relapse on day 79
0.10	3743	Relapse on day 16

* Chloroquine 0.5 mg/kg/base x 7 days was used as companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY (Page 6)
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 85/285

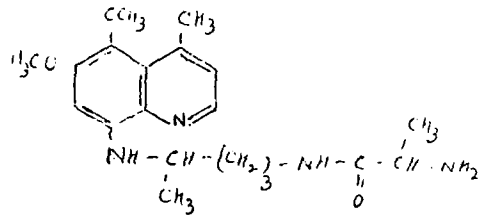
BN: I

DATE REC'D: 31-12-1985

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY #	RESULT
1.00	3613	Cured
1.00	3642	Cured
1.00	3643	Cured
0.316	3656	Relapse on day 25
0.316	3658	Relapse on day 15
0.316	3659	Relapse on day 17
0.10	3611	Cured
0.10	3651	Relapse on day 12
0.10	3657	Relapse on day 15

*Chloroquine 0.5 mg/kg(base) x 7 days was used as companion drug.

Date:12.1.87.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: CDRI 85/285

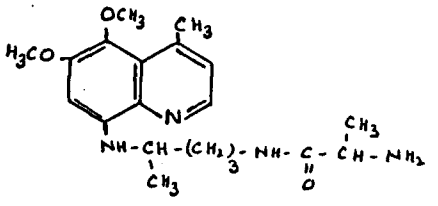
BN: IInd (Expt.2)

DATE REC'D: July 1986

QUANTITY: 500 mg

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg)	MONKEY #	RESULT
1.00	3845	Cured
1.00	3846	Cured
1.00	3848	Cured
0.316	3981	Cured
0.316	3997	Cured

CDRI PRIMATE ANTIMALARIA STUDY (Page 7)
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

BR: CDRI 86/5

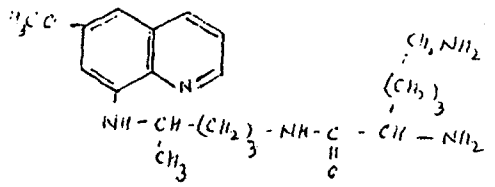
BN: I

DATE REC'D: 15-1-1986

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg)*	MONKEY #	RESULT
3.16	3735	Cured
3.16	3736	Cured
1.00	3737	Cured
1.00	3744	Cured
0.316	3751	Relapse on day 27
.316	3752	Relapse on day 22

*Chloroquine 0.5 mg/kg (base) x 7 days was used as companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

~~WR~~: CDRI 86/4

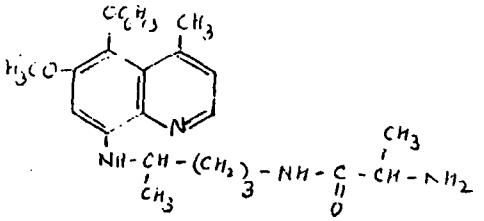
BN: I

DATE REC'D: 15- 1- 1986

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) Base *	MONKEY #	RESULT
1.00	3806	Cured
1.00	3807	Cured
0.316	3811	Cured
0.316	3817	Cured

*Chloroquine 0.5 mg/kg base x 7 days was used as companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

Date: 12.1.87.

~~NRx~~ CDRI/86/4

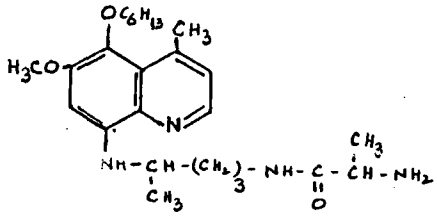
BN: IInd (Expt. 2)

DATE REC'D: July 1986

QUANTITY: 300 mg

VEHICLE: Methyl cellulose

ROUTE: Oral



RADICAL CURATIVE TESTing (7 day treatment)

DOSE (mg/kg)	MONKEY #	RESULT
1.00	4007	Cured
1.00	4009	Cured
0.316	3922	Cured
0.316	3924	Cured
0.316	4004	Relapse on day 59
0.10	3920	Cured
0.10	3996	Relapse on day 12

WR: CDRI 86/716

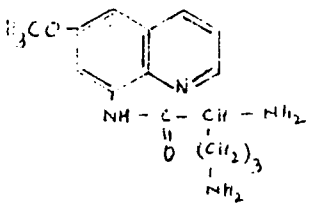
BN: I

DATE REC'D: 1-4-1986

QUANTITY: 300 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY #	RESULT
3.16	3809	Relapse on day 18
3.16	3819	Relapse on day 15
1.00	3843	Relapse on day 14
1.00	3844	Relapse on day 22

* Chloroquine @ 5 mg/kg base x 7 days was used as companion drug.

SEPT. 11, 1986

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

(Page 10).

~~WR~~ CDRI. 86/217

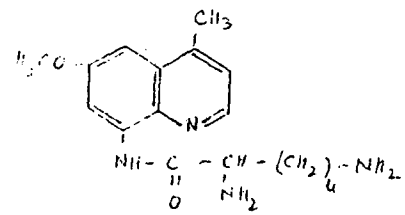
BN: I

DATE REC'D: 25-4-1986

QUANTITY: 300 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY #	RESULT
3.16	3819	Relapse on day 15
3.16	3823	Relapse on day 14
3.16	3825	Relapse on day 15

*Chloroquine @ 5 mg/kg base X 7 days was used as the companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 254715

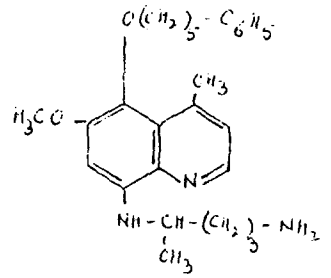
BN: BL 09293

DATE REC'D: December, '85

QUANTITY: 2 gm.

VEHICLE: Mwthyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY	RESULT
EXPT. I		
1.00	3684	Cured
1.00	3691	Cured
0.316	3696	Cured
0.316	3741	Cured
EXPT. II.		
0.316	3700	Cured
0.316	3750	Cured
0.10	3683	Cured
0.10	3693	Relapse on day 46

*Chloroquine > 5 mg/kg base x 7 days was used as the companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 254763

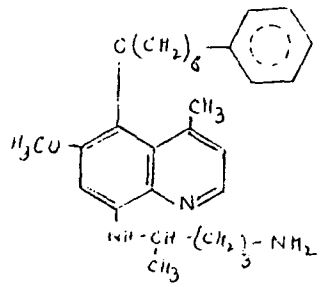
BN: BL 09962

DATE REC'D: DEC. '85

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) (Base) *	MONKEY	RESULT
EXPT. I		
1.00	3674	Cured
1.00	3689	Cured
0.316	3738	Cured
0.316	3737	Cured
EXPT. II		
0.316	3701	Cured
0.316	3702	Cured
0.10	3703	Relapse on day 36
0.10	3745	Relapse on day 50

*Chloroquine 0.5 mg/kg base was used as the companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 86/6

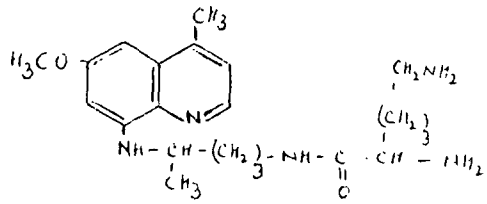
BN: I

DATE REC'D: 15-1- 1986

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: Oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY	RESULT
1.00	3819	Cured
1.00	3822	Cured
1.00	3827	Cured
0.316	3823	Cured
0.316	3824	Cured

* Chloroquine @ 5 mg/kg base X 7 days was used as the companion drug.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: CDRI 80/7

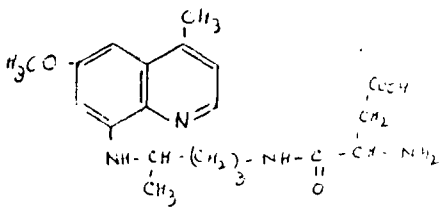
BN: I

DATE REC'D: 15- 1-1986

QUANTITY: 500 mg.

VEHICLE: Methyl Cellulose

ROUTE: oral



RADICAL CURATIVE TEST (7 day treatment)

DOSE (mg/kg) base *	MONKEY	RESULT
1.00	3980	Under test (No relapse till day 46)
1.00	3936	Relapse on day 12
1.00	4010	Relapse on day 20
0.316	4000	Relapse on day 13
0.316	4001	Relapse on day 13

*Chloroquine @ 5 mg/kg base x 7 days was used as the companion drug.

(Observations continuing)

Date: 12.1.87.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 238605

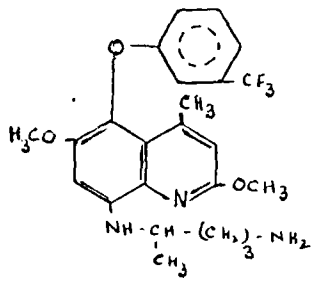
BN: BK 73252

DATE REC'D: Feb. 86

QUANTITY: 2 gm.

VEHICLE: Methyl cellulose

ROUTE: Oral.



RADICAL CURATIVE TESTING

DOSE (mg/kg)	MONKEY	RESULT
2.2 x 1 day	3915	Cured
2.2 x 1 day	3916	Cured
2.2 x 1 day	3917	Cured
0.316 x 7 day	3849	Cured
0.316 x 7 day	3850	Cured

Date: April 15, 1987

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 197236

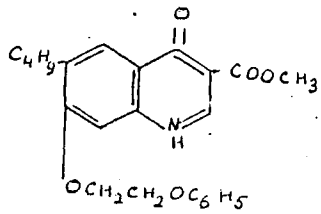
BR: BL 20274

DATE REC'D: Oct.'86

QUANTITY: 2 gm.

VEHICLE: -

ROUTE: Intra muscular



RADICAL CURATIVE TEST ING (7 day treatment)

DO... (mg/kg)	MONKEY #	RESULT
10.0	4348	Relapse on day 9
10.0	4350	Cured

Table 4: Causal prophylactic activity of primaquine in 9 day treatment schedule against sporozoite induced infections of *P.cynomolgi* in rhesus monkey

Dose mg/kg	No. of monkeys Protected/Treated	Days delay in onset of patency
1.00	4/4	Cured
2.00	4/4	Cured

Table 3: Causal prophylactic activity of primaquine in 3 day treatment schedule against sporozoite induced infections of *P.cynomolgi* in rhesus monkey.

Daily dose mg/kg	No. of monkeys Protected/Treated	Days delay in onset of patency
0.316	0/6	0,2,3,5,6,7
0.62	0/5	5,6,6,6,7
1.00	9/16	7,7,9,10,11,16,24
1.78	25/25	Cured
3.16	11/11	Cured
10.00	4/4	Cured

SEPT. 1[illegible]

(Pa[illegible])

CDRI PRIMARY SCREENING STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: PRIMAQUINE

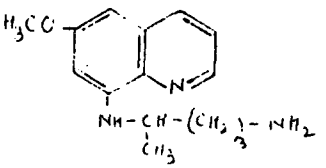
BN: SIGMA

DATE REC'D: DEC.'82

QUANTITY: 50 gm.

VEHICLE: MC

ROUTE: Oral



PROPHYLACTIC TEST (Single dose bioassay)

DOSE (mg/kg)	Treatment day	MONKEY NO.	RESULT
5.34	-2	3743	Patent on day 9
5.34	-2	3744	Patent on day 10
5.34	-1	3751	Patent on day 11
5.34	-1	3752	Patent on day 11
5.34	0	3749	Cured
5.34	0	3750	Cured
1.78	-1,0,+1	3753	[illegible] Cured [illegible]
Vehicle control		3705	Patent on day 8

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

XX: nCGJM 52

BN:

DATE REC'D: Oct. 1983

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

PROPHYLACTIC TEST (9 day test)

	DOSE (mg/kg) (base)	MONKEY #	RESULT
t.I	2.23	2241	Negative till day 70
	2.23	2242	Negative till day 70
	Control	2227	Patent on day 8
t.II	1.11	2328	Negative till day 70
	1.11	2330	Negative till day 70
	Control	2107	Patent on day 9
		2338	Patent on day 9

CLRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM [illegible]MOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

W: RCGJm 93 (= WR 199507)

P:

DATE RECD: Oct. 1983

QUANTITY:

VEHICLE: Normal saline/Methyl cellulose

ROUTE: Intravenous/Oral

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg) (base)	MONKEY #	RESULT
2.12	2243 (i.v.)	Toxic died after 2 doses
2.12	2244 (i.v.)	Toxic died after 2 doses
1.06	2203 (oral)	Patent on day 14
1.06	2205 (oral)	Patent on day 14
Control	2192	Patent on day 9

PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 199,507 (= RCGJM 53)

BN: ZP 13076

DATE REC'D: Dec. 1983

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY #	RESULT
10.00	2365	Patent on day 16
10.00	2366	Patent on day 17
3.16	2360	Patent on day 17
3.16	2363	Patent on day 16
1.00	2361	Patent on day 11
1.00	2369	Patent on day 11
.316	2367	Patent on day 11
.316	2368	Patent on day 11
Control	2327	Patent on day 9
	2378	Patent on day 9

CDRI PEPTIDE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

/A nCGJm 55 (= WR 250016)

[illegible]

DATE RECVD: Oct. 1983

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg) (base)	MONKEY #	RESULT
2.01	2233	Patent on day 15
2.01	2234	Patent on day 12
Control	2229	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

WR: 250,016 (= RCGTM 55)

BN: BK 69981

DATE REC'D: Dec. 1983

QUANTITY:

VEHICLE: methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY #	RESULT
10.0	2376	Patent on day 13
10.0	2377	Patent on day 13
3.16	2321	Patent on day 13
3.16	2379	Patent on day 12
1.00	2346	Patent on day 11
1.00	2399	Patent on day 11
.316	2400	Patent on day 11
.316	2401	Patent on day 11
Control	2327	Patent on day 9
		Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

XX: CDRI 83/472 (= WR 150811)

FM:

DATE RECVD:

QUANTITY:

VEHICLE: Normal saline

ROUTE: Intra-venous

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
1.35	2237	Patent on day 12
1.35	2238	Patent on day 12
Control	2229	Patent on day 9

(...)

[illegible] PRIVATE [illegible] STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SECONDARY INFECTED TEST ***

/#: 150,81 (= CDRI 83/172)

[illegible]: BE 21548

[illegible] RECVD: Dec. 1983

[illegible]NTITY:

VEHICLE: Methyl cellulose

[illegible]UTE: Oral

PROPHYLACTIC TEST (3 day test)

[illegible]OSE (mg/kg) (base)	MONKEY #	RESULT
10.00	2384	Patent on day 11
10.00	2306	Patent on day 11
3.16	2385	Patent on day 11
3.16	2387	Patent on day 11
1.00	2382	Patent on day 10
1.00	2383	Patent on day 11
0.316	2388	Patent on day 10
0.316	2389	Patent on day 9
Control	[illegible]	Patent on day 9
	2232	

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOL GI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

NR: RCGJm 33

PN:

DATE REC'D: Oct. 1983

QUANTITY:

VEHICLE: Normal saline/Methyl cellulose

ROUTE: Intra-venous/Oral

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
1.58	2235 i.v.	Patent on day 12
1.58	2236 i.v.	Patent on day 11
Control	2229	Patent on day 9
1.58	2329 oral	Patent on day 14
1.58	2331 oral	Patent on day 15
Control	2330	Patent on day 9
Control	2107	Patent on day 9

CDRI TEST NO. ANTIMALARIAL STUDY
PLASMODIUM BERGHEI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

XX: RCGJM 162

BN:

DATE RECVD: Oct. 1983

QUANTITY:

VEHICLE: Normal saline/Methyl cellulose

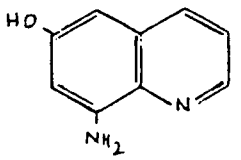
ROUTE: Intra-venous/Oral

PROPHYLACTIC TEST (9 dey test)

DOSE (mg/kg) (base)	MONKEY #	RESULT
2.94	2277 (i.v.)	Toxic; died after 4 doses
2.94	2278 (i.v.)	Toxic; died after 5 doses
1.47	2204 (oral)	Patent on day 13
1.47	2206 (oral)	Patent on day 13
Control	2192	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

CWR: 6890 (= RCGJM 161)



FN: ZP 38500

DATE REC'D: Dec. 1983

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
10.0	2392	No patency till day 60
10.0	2394	No patency till day 60
3.16	2391	Patent on day 14
3.16	2393	Patent on day 13
1.00	2390	Patent on day 13
1.00	2395	Patent on day 14
0.316	2397	Patent on dat 14
0.316	2398	Patent on day 14
Control	2396	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM [illegible]MOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

AK: CDRI 83/383

EN:

DATE REC'D:

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
3.25	2289	No patency till day 60
3.25	2290	No patency till day 60
1.62	2333	No patency till day 60
1.62	2335	No patency till day 60
0.51	2332	No patency till day 60
0.51	2334	No patency till day 60
Control	2230	Patent on day 9
	2338	Patent on day 9
	2107	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
*** SPOROZOITE INDUCED TEST ***

CDRI 83/382

EN:

DATE RECD:

QUANTITY:

VEHICLE: Methyl cellulose

ROUTE: Oral

PROPHYLACTIC TEST (9 day test)

DOSE (mg/kg)(base)	MONKEY #	RESULT
3.25	2286	No patency till day 60
3.25	2288	No patency till day 60
3.25	2325	No patency till day 60
3.25	2337	No patency till day 60
1.62	2320	No patency till day 60
1.62	2322	No patency till day 60
0.51	2326	No patency till day 60
0.51	2334	No patency till day 60
Control	2230	Patent on day 9
	2338	Patent on day 9
	2107	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 242511

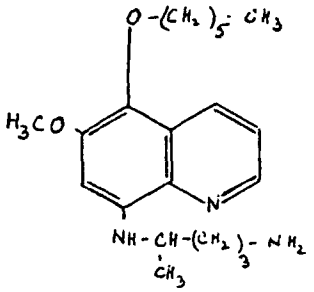
BN: BJ 78592

DATE REC'D: Dec. 1982

QUANTITY: 2 Gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST

DOSE (mg/kg) (base)	MONKEY NO.		RESU
1.78	2700	No patency till day 70	
1.78	2701	No patency till day 70	
1.00	2702	No patency till day 70	
1.00	2703	No patency till day 70	
0.316	2704	No patency till day 70	
0.316	2705	No patency till day 70	
0.10	2720	No patency till day 70	
0.10	2722	No patency till day 70	
Vehicle control	2644	Patent on day 8	

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

NR: 242511 (Revalidation results)

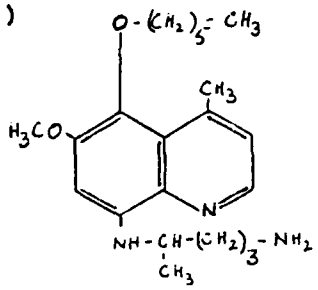
B: BJ 78592

DATE REC'D: DEC. 1982

QUANTITY: 2 Gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
0.316	2895	No patency till day 70
0.316	2896	No patency till day 70
0.10	2897	No patency till day 70
0.10	2898	No patency till day 70
0.10	2899	No patency till day 70
0.10	2900	No patency till day 70
0.10	2901	No patency till day 70
0.0316	2902	Patent on day 18
0.0316	2903	Patent on day 13
Vehicle control	2812	Patent on day 10

CDRI POTENTIAL ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 242511

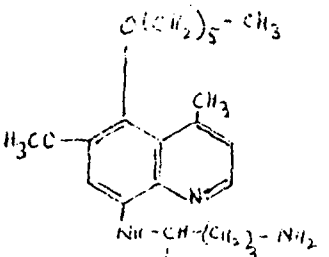
BN: EJ 78592

DATE RLC'D: DEC.,'82

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (Single Dose bioassay)

DOSE (mg/kg)	Treatment day	MONKEY NO.	RESULT
0.300	-2	3738	Patent on day 9
0.300	-2	3739	Patent on day 10
0.300	-1	3674	Patent on day 12
0.300	-1	3741	Patent on day 10
0.300	0	3740	Patent on day 13
0.300	0	3642	Patent on day 14
Vehicle control		3705	Patent on day 8

Oral [illegible]
PLASMODIUM CYNOMOLGI [illegible]
SPOROZOITE [illegible]

NR: 242511

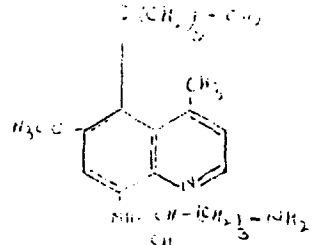
IBN: 09417

DATE REC'D: Feb. '58

QUANTITY: 2 gm

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (Single dose bioassay)

DOSE (mg/kg)	Treatment Day	MONKEY NO.	RESULT
.95	-5	40 [illegible]	Patent on day 11
3.95	-5	[illegible]	Patent on day 11
[illegible].95	-3	[illegible]	Patent on day 10
[illegible].95	-3	[illegible]	Patent on day 10
.95	0	39[illegible]	Cured
[illegible].95	0	[illegible]	Cured
Vehicle Control		39[illegible]	Patent on day 8
		3995	Patent on day 8

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 225448

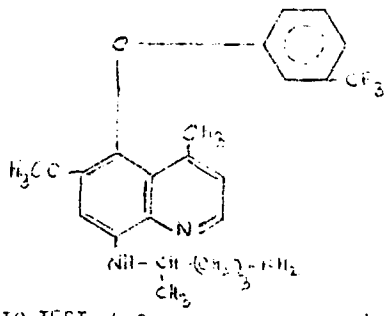
IN: DR 50622

DATE REC'D: 10.10.1984

QUANTITY: 5 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day treatment)

DOSE (mg/kg)	MONKEY NO.	RESULT
0.316	3695	Cured
0.316	3695	Cured
0.316	3696	Cured
0.316	3700	Cured
0.316	3702	Cured
0.10	3693	Patent on day 20
0.10	3698	Patent on day 15
0.10	3701	Cured
0.10	3704	Patent on day 16
0.10	3705	Patent on day 16
0.0316	3694	Patent on day 12
0.0316	3699	Patent on day 13
0.0316	3691	Patent on day 14
0.0316	3697	Patent on day 24
0.0316	3703	Cured
Vehicle control	3688	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

SR: 225448

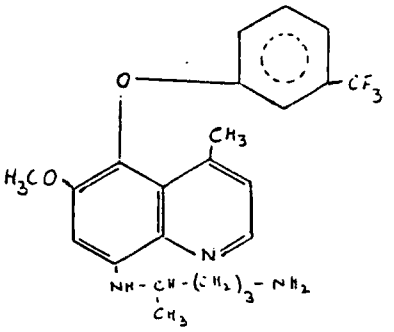
GN: 585222

DATE REC'D: 10.10.84

QUANTITY: 5 Gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
1.78	2875	No patency till day 70
1.78	2876	No patency till day 70
1.00	2877	No patency till day 70
1.00	2878	No patency till day 70
0.316	2879	No patency till day 70
0.316	2880	No patency till day 70
0.10	2881	No patency till day 70
0.10	2882	No patency till day 70
Vehicle control	2811	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI — RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 225448

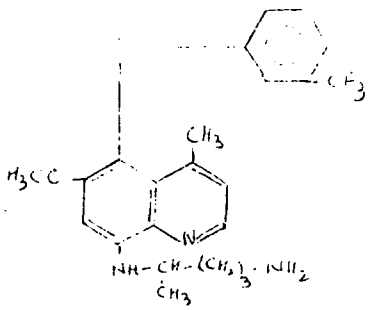
BR: 2F 45514

DATE REC'D: FEB '86

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (Single dose bioassay)

DOSE (mg/kg)	Treatment on day	MONKEY NO.	RESULT
2.84	-5	3985	Patent on day 17
2.84	-5	3988	Patent on day 13
2.84	-3	3987	Cured
2.84	-3	3996	Cured
2.84	0	3991	Cured
2.84	0	4007	Cured
Vehicle control		3990	Patent on day 8

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 238605

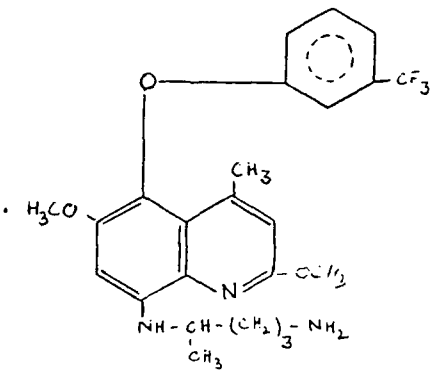
BK 73252

DATE REC'D: 10.10.1984

QUANTITY: 5 Gms.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
1.78	2887	No patency till day 70
1.78	2888	No patency till day 70
1.00	2885	No patency till day 70
1.00	2886	No patency till day 70
0.316	2883	No patency till day 70
0.316	2884	No patency till day 70
0.10	2835	Patent on day 17
0.10	2836	No patency till day 70
Vehicle control	2811	Patent on day 9.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 238605 (Revalidation results)

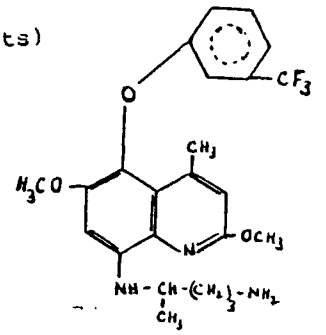
LN: BK 73252

DATE REC'D: 10.10.1984

QUANTITY: 5 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) base	MONKEY NO.	RESULT
0.316	3279	No patency till day 70
0.316	3280	No patency till day 70
0.316	3282	No patency till day 70
0.316	3283	No patency till day 70
0.316	3201	No patency till day 70
0.10	3195	Patent on day 8
0.10	3213	Patent on day 8
0.10	3214	Patent on day 8
0.10	3219	Patent on day 8
0.10	3284	Patent on day 8
0.0316	3215	Patent on day 8
0.0316	3218	Patent on day 8
0.0316	3221	Patent on day 8
0.0316	3281	Patent on day 8
Vehicle control	3199	Patent on day 8
	3205	Patent on day 8

CDRI PREDATE SCREEN STUDY
PLASMODIUM CYNOMOLGI IN RHESUS MONKEY

SUBCUTANEOUS ROUTE TEST

AR: 236605

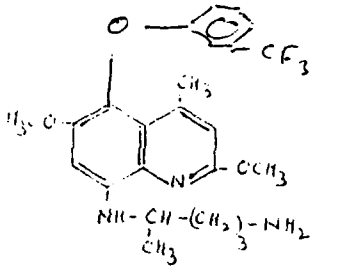
BK: BK 73252

DATE REC'D: 10.10.1984

QUANTITY: 5 gm.

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (Single dose bioassay)

DOSE (mg/kg)	Treatment day	MONKEY NO.	RESULT
0.948	-2	3694	Patent on day 10
0.948	-2	3696	Patent on day 11
0.948	-1	3735	Patent on day 12
0.948	-1	3736	Patent on day 11
0.948	0	3737	Patent on day 12
0.948	0	3745	Cured
Vehicle control		3705	Patent on day 8

CDRI PRIMARY SCREENING ORAL STUDY
PLASMODIUM CYNOMOLGI : RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 239605

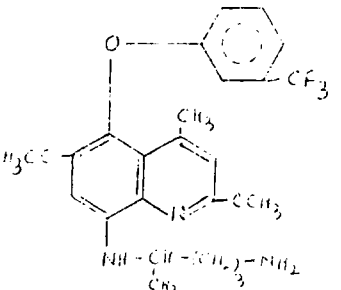
BH: SM 73252

DATE REC'D: FEB. '66

QUANTITY: 2 gm

VEHICLE: Methyl Cellulose

ROUTE: Oral

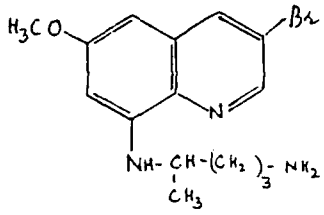


PROPHYLACTIC TEST (Single dose bioassay)

DOSE (mg/kg)	Treatment on day	MONKEY NO.	RESULT
2.84	-5	3994	Patent on day 11
2.84	-5	3984	Patent on day 14
2.84	-3	3993	Patent on day 16
2.84	-3	4006	Cured
2.84	0	4004	Cured
2.84	0	4009	Cured
Vehicle control		3990	Patent on day 8

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

CDRI RCG9 (Bromo-primaquine)



DATE REC'D: July, 1984

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: oral

PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) (base)	MONKEY NO.	RESULT
3.16	2714	Patent on day 19
3.16	2715	No patency till day 70
1.00	2723	Patent on day 16
1.00	2724	Patent on day 18
Vehicle control	2644	Patent on day 8.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 249420

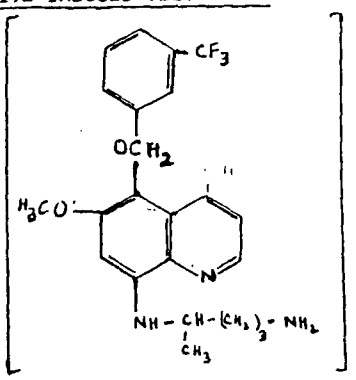
BN: BK 56537

DATE REC'D: 10.10.1984

QUANTITY: 2 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)	MONKEY NO.	RESULT
1.78	2955	No patency till day 70
1.78	2956	No patency till day 70
1.00	2957	No patency till day 70
1.00	2958	No patency till day 70
0.316	2959	No patency till day 70
0.316	2960	No patency till day 70
0.10	2961	No patency till day 70
0.10	2962	No patency till day 70
Vehicle control	2964	Patent on day 9

CDRI PRIMARY ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 249420

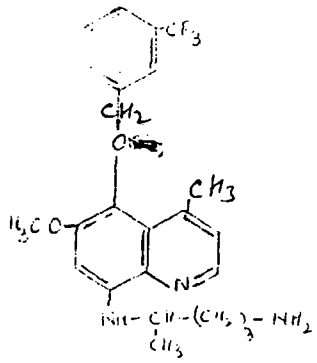
BH: BH 56537

DATE REC'D: Oct. '84

QUANTITY: 2 gm.

VEHICLE: Methyl Cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day treatment)

DOSE (mg/kg)	MONKEY NO.	RESULT
0.316	3816	Cured
0.316	3818	Cured
0.10	3819	Patent on day 14
0.10	3820	Patent on day 12
0.0316	3815	Patent on day 10
0.0316	3817	Patent on day 9
Vehicle control	3810	Patent on day 8
	3812	Patent on day 6

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKLY

SPOROZOITE INDUCED TEST

WR: 7295

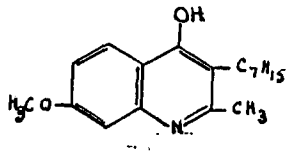
BN: ZN 37017

DATE REC'D: May 1985

QUANTITY: 6 gm.

VEHICLE: Methylcellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)	MONKEY NO.	RESULT
10.0	3351	Patent on day 12
10.0	3352	Patent on day 19
3.16	3353	Patent on day 10
3.16	3354	Patent on day 10
1.00	3338	Patent on day 10
1.00	3355	Patent on day 10
Vehicle control	3142	Patent on day 6

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 93133

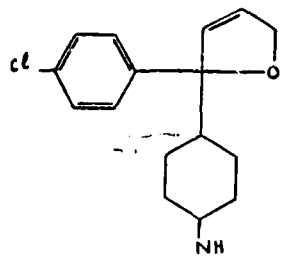
DN: ZN 07395

DATE REC'D: May, 1985

QUANTITY: 1 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg)	MONKEY NO.	RESULT
10.00	3337	Patent on day 12
10.00	3340	Patent on day 11
3.16	3339	Patent on day 10
3.16	3333	Patent on day 10
1.00	3336	Patent on day 9
1.00	3350	Patent on day 10
Vehicle control	3142	Patent on day 8.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 194905

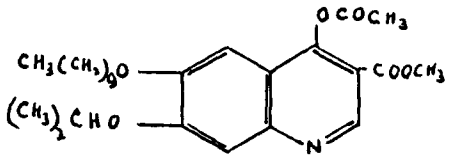
DN: ZP 45041

DATE REC'D: May, 1985

QUANTITY: 5 gm.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) base	MONKEY NO.	RESULT
10.00	3369	Patent on day 23
10.00	3359	Patent on day 30
3.16	3371	Patent on day 22
3.16	3373	Patent on day 13
1.00	3358	Patent on day 12
1.00	3370	Patent on day 14
Vehicle control	3367	Patent on day 9.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 190729

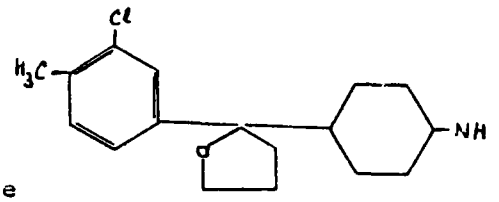
BN: ZP 45765

DATE REC'D: May, 1985

QUANTITY: 500 mg.

VEHICLE: Methyl cellulose

ROUTE: oral



PROPHYLACTIC TEST (3 day test)

DOSE (mg/kg) base	MONKEY NO.	RESULT
10.00	3357	Patent on day 19
10.00	3362	Patent on day 17
3.16	3361	Patent on day 12
3.16	3365	Patent on day 13
1.00	3360	Patent on day 10
1.00	3366	Patent on day 13
Vehicle control	3367	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 158124

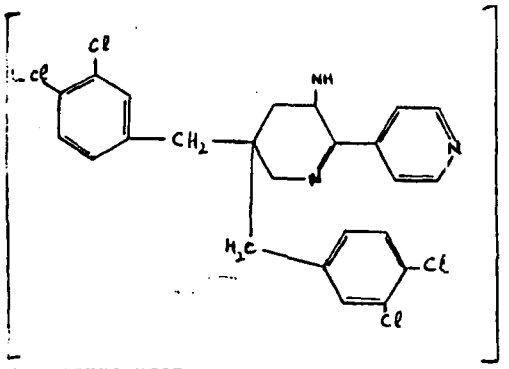
BN: BD 22997

DATE REC'D: May, 1985

QUANTITY: 3950 mg

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST

DOSE (mg/kg) base	MONKEY NO.	RESULT
10.0	3455	Patent on day 12
10.0	3461	Patent on day 12
3.16	3453	Patent on day 11
3.16	3458	Patent on day 11
1.00	3452	Patent on day 10
1.00	3462	Patent on day 10
Vehicle control	3456	Patent on day 9

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKLY

SPOROZOITE INDUCED TEST

WR: 214235

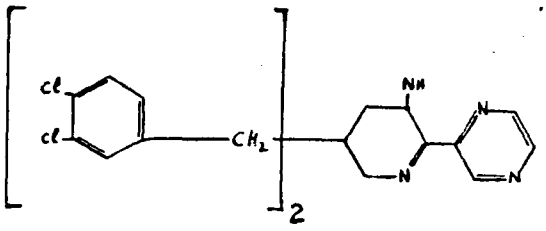
BN: BE 14570

DATE REC'D: May, 1985

QUANTITY: 350 mg

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST

DOSE (mg/kg) base	MONKLY NO.	RESULT
3.16	3457	Patent on day 12
3.16	3460	Patent on day 10
1.00	3459	Patent on day 11
1.00	3463	Patent on day 11
Vehicle control	3456	Patent on day 9.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY

SPOROZOITE INDUCED TEST

WR: 226626

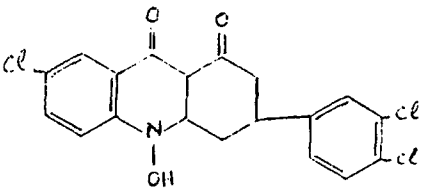
UN: ZP 29421

DATE REC'D: May, 1985

QUANTITY: 378 mg.

VEHICLE: Methyl cellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day treatment)

DOSE (mg/kg)	MONKEY NO.	RESULT
10.0	3554	Patent on day 9
10.0	3555	Patent on day 10
3.16	3552	Patent on day 9
3.16	3553	Patent on day 10
1.00	3508	Patent on day 9
1.00	3511	Patent on day 9
Vehicle control	3501	Patent on day 8

(Luxcivine)

[illegible]

[illegible]

[illegible]

AR: 249252

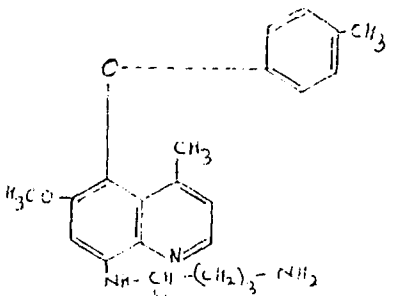
IM: EJ 76365

DATE REC'D: Dec. '82

QUANTITY: 2 gm.

VEHICLE: MethylCellulose

ROUTE: Oral



PROPHYLACTIC TEST (3 day Treatment)

DOSE (mg/kg)	MONKEY NO.	RESULT
0.316	3803	Patent on day 19
0.316	3809	Patent on day 14
0.10	3811	Patent on day 11
0.10	3814	Patent on day 11
0.0316	3806	Patent on day 10
0.0316	3807	Patent on day 9
Vehicle control	3810	Patent on day 8
	3812	Patent on day 8

Date: 12.1.87.

CDRI PRIMATE ANTIMALARIAL STUDY
PLASMODIUM CYNOMOLGI - RHESUS MONKEY
SPOROZOITE INDUCED TEST

WR: 197236

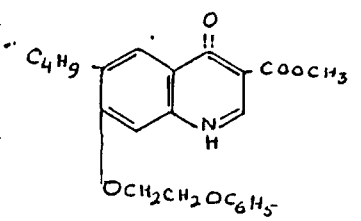
BN: BL 20274

DATE REC'D: Oct. 1986.

QUANTITY: 2 gm.

VEHICLE:

ROUTE: Intra musculer



PROPHYLACTIC TEST

DOSE (mg/kg)	MONKEY	RESULT
31.6	4354	Cured
31.6	4355	Cured
10.0	4356	Patent on day 12
10.0	4357	Patent on day 33